Neurophysiological signals of genetic liability, disease onset and progression in psychosis

Constante, Miguel De Sequeiros

Awarding institution:
King's College London

Neurophysiological signals of genetic liability, disease onset and progression in psychosis

Miguel Constante

Institute of Psychiatry
King's College London
University of London

A thesis submitted in fulfilment of the requirement for the degree of
Doctor of Philosophy in King's College London,
University of London
January 2016

ABSTRACT

BACKGROUND: Event-Related Oscillations (EROs) have been linked to cognition and found to be abnormal in psychotic disorders. It is unclear if EROs abnormalities reflect genetic liability to psychosis, if they are markers of onset and/or progression of the disease. **METHODS:** 35 early psychosis and 44 chronic psychosis patients, 69 unaffected first-degree relatives, 40 subjects with an 'at risk mental state' (ARMS) and 76 healthy controls were included in this study. Subjects underwent electroencephalography recording during an auditory oddball task, a duration-deviant passive auditory oddball paradigm, and a paired-click paradigm, which elicit, respectively, selective attention, salience detection and sensory gating brain processes. Wavelet-based time-frequency analyses were conducted to extract single trial EROs. Relevant EROs clusters were identified by examining EROs condition effects, EROs associations with oddball task reaction time and EROs differences between patients and controls, through cluster-based t-tests and regression analysis. Composite EROs were compared between groups using ANOVA, regressed to test relationships between the three paradigms and associations with psychosis symptoms scores. **RESULTS:** Selective attention EROs were influenced by psychosis disease progression, salience EROs by disease chronicity and sensory EROs gating by disease onset. These three EROs groups were all influenced by psychosis genetic liability. Psychosis symptoms were predicted by sensory EROs gating and salience EROs in early and chronic patients, respectively. Salience EROs and EROs gating combined, predicted selective attention EROs in all groups, except in psychosis patients. First-degree relatives and ARMS subjects showed evidence of compensatory EROs changes. Salience EROs decreased with advancing age. **CONCLUSIONS:** In psychosis, attention-related EROs reflect genetic vulnerability, disease onset and progression, together with brain compensatory adaptations and ageing.

DECLARATION OF CONTRIBUTIONS AND

ACKNOWLEDGEMENTS

As part of my PhD, I undertook and led most of the tasks presented in this thesis, covering all the steps in this work: from literature review and study design, through the recruitment of participants, clinical diagnostic interviews and application of scales, lab testing, EEG processing, statistical analysis and papers/thesis writing up. I learnt the skills to carry out all of these tasks independently. I also collaborated with colleagues in their PhD data collection and in the review of their papers manuscripts, within related research topics, leading to my co-authorship in published papers. The contributions to my thesis are summarised in Table 1.1 and the published papers I have co-authored are listed in Table 1.2.

Table 1.1 | Breakdown of contributions to the thesis

Sample	Early psychosis patients (n=35)	ARMS (n=40)	Chronic psychosis patients (n=44)	1st degree Relatives (n=69)	Controls (n=76)	Total (n=264)
Recruitment	**MC**	IW, MS	MC, IW, C.C, MS	MC, IW, C.C, MS	MC, IW, C.C, MS	
Data collection	MC	IW, MS	MC, IW, MS	MC, IW, MS	MC, IW, MS	
EEG testing	MC	IW, MS	IW, MS	IW, MS	MC, IW, MS	
Clinical assessments	MC		MC, AD			
Data analysis			MC			
Writing up (PhD papers and thesis)			MC			

MC - **Miguel Constante**, IW - Ian Williams, M.S - Madiha Shaikh, C.C - Chris Chaddock, A.D - Anirban Dutt

Table 1.2 | Co-authorship in published papers

1. Ranlund, S., J. Nottage, M. Shaikh, A. Dutt, **M. Constante**, M. Walshe, M. H. Hall, K. Friston, R. Murray and E. Bramon (2014). "Resting EEG in psychosis and at-risk populations--a possible endophenotype?" Schizophr Res **153**(1-3): 96-102.

2. Shaikh, M., M. H. Hall, K. Schulze, A. Dutt, K. Li, I. Williams, M. Walshe, **M. Constante**, M. Broome, M. Picchioni, T. Toulopoulou, D. Collier, D. Stahl, F. Rijsdijk, J. Powell, R. M. Murray, M. Arranz and E. Bramon (2013). "Effect of DISC1 on the P300 waveform in psychosis." Schizophr Bull **39**(1): 161-167.

3. Dutt, A., T. Ganguly, M. Shaikh, M. Walshe, K. Schulze, N. Marshall, **M. Constante**, C. McDonald, R. M. Murray, M. P. Allin and E. Bramon (2012). "Association between hippocampal volume and P300 event related potential in psychosis: support for the Kraepelinian divide." Neuroimage **59**(2): 997-1003.

4. Crossley, N. A., **M. Constante**, P. Fusar-Poli and E. Bramon (2012). "Neurophysiological alterations in the prepsychotic phases." Curr Pharm Des **18**(4): 479-485.

5. Shaikh, M., M. H. Hall, K. Schulze, A. Dutt, M. Walshe, I. Williams, M. **Constante, M**. Picchioni, T. Toulopoulou, D. Collier, F. Rijsdijk, J. Powell, M. Arranz, R. M. Murray and E. Bramon (2011). "Do COMT, BDNF and NRG1 polymorphisms influence P50 sensory gating in psychosis?" Psychol Med **41**(2): 263-276.

6. Crossley, N. A., **M. Constante**, P. McGuire and P. Power (2010). "Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis." Br J Psychiatry **196**(6): 434-439.

I would like to thank all patients who agreed to take part in this study. In doing data collection and clinical interviews, I was often impressed by how, despite undergoing strife in their lives at that time, these people agreed to focus on their experiences and be subject to testing, most often with a clear altruistic motivation.

I am grateful to Ian Williams, Madiha Shaikh, Anirban Dutt and Chris Chaddock, whom I shared with part of the task of recruiting/assessing participants. This involved much letter sending, phone calling, trips as far as the South Coast of England, challenging interactions... all of which I believe made us grow and left us with fond memories. My colleagues also made available to me neurophysiological and clinical data they collected for their own research work.

I am thankful to the Donders Institute group in Nijmegen for sharing their work with the scientific community creating Fieldtrip, the EEG analysis software I used, and organizing their teaching course, which I attended and was very valuable in learning about EEG data processing and statistical analysis.

It has been a privilege to work under the supervision of Elvira Bramon and Robin Murray. I must express my thanks to Elvira for her encouragement, constructive criticism and Robin for his overarching perspective on theory and research practice in psychiatry. I also had the opportunity to contact and work with a wide community of researchers at the IoP, learn from different lines of research, which has been a most enriching experience.

I am deeply grateful to my wife Ana, my parents Antonio and Lucinda, my sister Joana, without their support I would not have been able to take this work to conclusion. I would like to dedicate this PhD to my beloved daughters, Inês and Rita.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE – INTRODUCTION

1.1 Neurodevelopmental and neurodegenerative models of schizophrenia

The understanding of schizophrenia's etiopathology and natural course, which shape its clinical presentation and guide its treatment, can be viewed under two different perspectives: the neurodevelopmental and neurodegenerative models. The **neurodevelopmental model** of schizophrenia posits that this disease is the outcome of abnormalities in maturational processes, occurring in the brain long before the onset of symptoms, caused by genetic and environmental factors (Rapopport *et al*. 2012, Murray and Lewis 1987, Weinberger 1987). Patients show a neurodevelopmental lag, gradually falling behind, in cognitive ability, probably until early adulthood (Reichenberg *et al*. 2010). In the neurodevelopmental model, genetic liability to psychosis plays a central role, particularly those genes involved in brain development. In order to unravel the complex genetics of psychiatric disorders, the concept of **endophenotypes** has been construed (Flint and Munafo 2014, Glahn *et al*. 2014, Kendler and Neale 2010, Turetsky *et al.* 2007, Cannon and Keller 2006, Gottesman and Gould 2003). Endophenotypes are disease associated objective measures, including neurophysiological, neuroanatomical, biochemical, endocrinological and neuropsychological parameters. They should reflect the action of susceptibility genes more directly than the disease phenotypical expression, increasing the power to identify those genes and also to understand the mechanisms whereby they influence psychiatric disorders. The criteria for evaluating a potential endophenotype are established, with some variations between authors. The trait should be associated with the disorder in the

general population, be more prevalent in unaffected relatives of affected individuals than in the general population, co-segregate with the disease in families, be heritable, be reliably measured, be stable and state-independent (i.e. it should be present in affected individuals even outside periods of acute illness or symptom exacerbation), its measurement should be non-invasive and economically feasible. This approach has been extensively applied to schizophrenia (Allen *et al*. 2009, Braff *et al*. 2007) with large ongoing multicentre studies (Greenwood *et al.* 2013, Calkins *et al*. 2007).

With a different focus, the classic **Kraepelin model of schizophrenia** stressed that **neurodegenerative** changes take place after the onset of symptoms, with gradual decline in brain, cognitive and social functioning (Lieberman 1999). It has been argued that relapse in schizophrenia is linked with disease progression (Emsley *et al*. 2013). Neuroimaging studies indicate progressive neuroanatomical changes in schizophrenia, even though these may be confounded by other factors, including medication effects (Haijma *et al*. 2013, Bora *et al*. 2011, Chan *et al.* 2011, Olabi *et al.* 2011, Leung *et al*. 2011, Ellison-Wright *et al.* 2008, Hulshoff and Kahn 2008, Wood *et al.* 2008). The neurodegenerative hypothesis is also supported by the evidence of better treatment response in first-episode schizophrenia patients, compared to chronic multi-episode schizophrenia (Kahn *et al*. 2008, Jäger *et al*. 2007, Lieberman *et al*. 1993, McEvoy *et al*. 1991). Against this hypothesis, however, meta-analyses of longitudinal studies of cognition in schizophrenia have indicated there is no progressive cognitive impairment and that, in fact, improvement is possible after the onset of the disorder (Lewandowski *et al.* 2011, Szöke *et al*. 2008). It has been argued (Zipursky *et al*. 2012) that: 1) longitudinal studies indicate few patients show incremental loss of function that is characteristic of neurodegenerative disorders; 2) decreases in brain tissue volumes reported in neuro-imaging studies could be explained by the effects of antipsychotic

medication, substance abuse, effects of lifestyle or elevated glucocorticoid levels associated with chronic stress; and 3) the deterioration that occurs in some patients could reflect poor access or adherence to treatment, the effects of concomitant conditions, and social and financial impoverishment.

The **clinical staging model of psychosis** (McGorry *et al*. 2006) makes the assumption that neurobiological deficits show progression and transgression of thresholds, in time, through different stages of psychosis. This is proposed to be a more refined form of diagnosis, which could promote early intervention and improve the logic and timing of therapeutic interventions. These interventions could be evaluated in terms of their ability to prevent or delay progression from earlier to later stages of disorder, and they could be selected on clear-cut risk/benefit criteria. This model identifies a critical period, the first 5 years after the first episode of psychosis. This early psychosis stage is considered non specific, with phenotypal overlap, variable prognosis and this group of patients can follow several diagnostic trajectories on follow up. In this context, biomarkers correlating with psychosis severity could allow us to stage the disease, provide insights into treatment and prognosis (Light *et al.* 2012, Luck *et al.* 2011). Moving the field even further, in recent years much research has been made on the psychosis high risk state (Fusar-Poli *et al*. 2013), trying to identify individuals at high risk of coming do develop a full blown psychotic episode. The attenuated psychosis syndrome, a syndrome characterized by sub-threshold psychotic symptoms, associated with a very significant increase in the risk of development of a full-fledged psychotic disorder (schizophrenia spectrum, psychotic mood disorder, and other psychotic disorders) within the next year, has been included as a nosological category in DSM-5, as a condition for further study (Tsuang *et al.* 2013). Operationalized diagnostic criteria have given rise to the ultra high risk (Yung *et al*. 2003), clinical high risk (Cornblatt *et al*. 2003) or at-risk mental state (ARMS; Yung *et al*. 1996) status. These criteria require

the presence of 'attenuated' psychotic symptoms, full-blown psychotic symptoms that are brief and self-limiting (Brief Intermittent Psychotic Symptom syndrome, BLIPS), or a significant decrease in functioning in the context of a genetic risk for schizophrenia (Genetic Risk and Deterioration syndrome, GRD). Despite the operationalization of these diagnostic criteria and identification of other risk factors (Fusar-Poli *et al.* 2013, Mason *et al*. 2004), their positive predictive value in predicting transition to psychosis declined (Yung *et al*. 2007). There is evidence that early psychological and pharmacological interventions may improve outcomes (Stafford *et al*. 2013), however the evidence is still not conclusive and the risk-benefit ratio of for example starting antipsychotic treatment in the prodromal phase raises controversy (Weiser 2011). Again, the identification of **biomarkers**, in this case associated with a subsequent transition to psychosis, would be valuable in targeting treatment to those who require it. There are possible candidates: neuropsychological functioning in clinical high risk individuals has been shown to be significantly lower in those who progressed to psychosis, than in those who did not and was worst in the subgroup with a family history of psychosis (Seidman *et al*. 2010); individuals at high risk for psychosis show MRI alterations in regional gray matter volume regardless of whether they subsequently develop the disorder and in this population, reduced left parahippocampal volume has been specifically associated with the later onset of psychosis (Mechelli *et al*. 2011); patterns of abnormalities in attention dependent (Van Tricht *et al*. 2011) and pre-attentive (Hsieh *et al*. 2012) auditory event-related potentials, in subjects across different risk levels of psychotic disorders have been described.

The **endophenotype and neurodegenerative/progressive models** are two approaches with, in the first instance, somewhat contradictory assumptions. The endophenotype model focuses on heritability, familial association, cosegregation and state-

independence. Endophenotypes are regarded as constant traits, which are present at all clinical stages, even in the non clinical at risk state. State markers, on the contrary, should depend on the stage of the illness, intensity of symptoms, medication status and other clinical aspects. The distinction between endophenotypes and state markers may, however, not be so clear cut. As an example, P300 ERP amplitude reduction has been shown in asymptomatic schizophrenia patients and unaffected relatives of patients; however, P300 amplitude deficits can also track symptoms fluctuation and show increase in magnitude with advancing chronicity of the disease, as reviewed below.

1.2 The psychosis continuum

In the last few decades, there has been a trend in diagnostic classification and research to focus on the broader category of psychosis, **across the traditional Kraepelian diagnostic classifications**, including schizophrenia and bipolar affective disorder. Abandoning the categorical approach in favour of a dimensional or continuous conceptualization has long been proposed (Crow 1990) and the latter has been integrated in DSM V (Barch *et al*. 2013). This is based both on the observations, in clinical practice, of a phenotypic overlap between the diagnostic categories, as well as on the available empirical data linking these disorders. Symptoms, psychosocial functioning, and familial lineage have been found to show considerable overlap across the schizophrenia, schizoaffective disorder and bipolar I disorder (Tamminga *et al*. 2013). Common genetic liability between these disorders has been established (Craddock and Owen 2010, Lichtenstein *et al*. 2009, Murray *et al*. 2004, Cardno *et al*. 2002). Schizoaffective disorder may bridge genetic liability to both a mood disorder and schizophrenia (Bramon and Sham 2001). Other aetiological risk factors, including preterm birth (Nosarti *et al*. 2012) may well act across these traditional diagnostic

boundaries. With regards to their neurophysiology, evidence suggests these disorders have both shared and specific abnormalities (Ethridge *et al*. 2012, Hamm *et al*. 2012, Thaker 2008). Schizophrenia and bipolar disorder patients share a similar cognitive impairment profile, but different degrees of deficits, where patients with schizophrenia do worse: the difference between the two groups seems to be more quantitative (degree of deficit) rather than qualitative (profile) (Vöhringer *et al*. 2013). A generic association between genetic risk for those disorders and MRI white matter volume reduction in the left frontal and temporoparietal regions has been reported (McDonald *et al*. 2004). Moreover, a meta-analysis comparing MRI abnormalities in schizophrenia and bipolar disorders found those abnormalities not to be diagnostically specific (Arnone *et al*. 2009). There are ongoing efforts through multicentre studies to find intermediate phenotypes across psychotic disorders (Tamminga *et al*. 2013, Psychosis Endophenotypes International Consortium and the Wellcome Trust Case-Control Consortium 2, 2013). There is also overlap between non affective and affective psychosis treatments, such that antipsychotics are effective not just for schizophrenia but also bipolar disorder (Fountoulakis *et al*. 2012). Diagnostic category barriers have been cut across the schizophrenia diagnosis itself: The American Psychiatric Association, in their new classification of psychiatric disorders, the DSM V, abandoned the schizophrenia subtypes (paranoid, disorganized, catatonic, undifferentiated, and residual type), considering their limited diagnostic stability, low reliability and poor validity. According to APA, those subtypes did not appear to help with providing better targeted treatment, nor predicting treatment response (Tandon *et al*. 2013).

1.3 P300, MMN and P50 Event-Related Potentials (ERPs) in psychosis

ERP biomarkers have several desirable properties to measure neural events underlying cognition, aiding to identify endophenotypes, defining treatment targets, evaluating new compounds in animals and in humans and for identifying individuals who are good candidates for early interventions or for specific treatments (Luck *et al*. 2011): (1) they provide a direct measure of electrical activity during neurotransmission; (2) their high temporal resolutions make it possible to measure neural synchrony and oscillations; (3) they are relatively inexpensive and convenient to record; (4) animal models are readily available for several ERP components; (5) decades of research has established the sensitivity and reliability of ERP measures in psychiatric illnesses; and 6) feasibility of large N (>500) multisite studies has been demonstrated.

Abnormalities in the auditory ERP components, P300 (Turetsky *et al.* 2015, Bramon *et al*. 2004), Mismatch Negativity (MMN) (Light *et al.* 2015, Umbricht *et al*. 2005, Bramon *et al*. 2004) and P50 gating (Olincy *et al*. 2010, Patterson *et al*. 2008, Bramon *et al*. 2004) have been associated to schizophrenia (Turetsky *et al*. 2007, Van der Stelt and Belger 2007). They have also been implicated in bipolar disorder, although MMN impairment has been more specifically linked to schizophrenia (Thaker 2008).

The auditory ERPs are believed to have specific functional significance, which can be associated to different brain processes that are impaired in psychosis and bear clinical significance (Turetsky *et al*. 2009). **P300** can be elicited in the auditory "oddball" paradigm and is a brain response to task-relevant, context dependent, stimuli. In the classical experimental design, the subject is asked to attend to 2 different types of auditory stimuli, low Vs high frequency clicks, one which is frequent, the other rare and is instructed to respond to the rare stimulus (target) by pressing a button. This generates an ERP with a positive polarity wave approximately 300 ms post stimulus, the P300

wave. It is thought to index stimulus significance - the degree of **selective attention** allocated to the eliciting stimuli and memory updating operations in the brain (Polich 2007, Roth and Cannon 1972, Sutton *et al.* 1965). **MMN** is elicited in a "passive" auditory oddball paradigm, to infrequent deviant stimuli. The subject is resting or involved in the attentive processing of visual information, but not the auditory stimuli, hence the "passive" designation. It is essentially an automatic, pre-attentive brain response and it is believed to reflect the comparison process between the current deviant acoustic input and a sensory memory trace representing the physical features of the preceding standard stimuli. It represents the initial stage of the alerting and redirecting of the organism's attention towards **salient** or deviant, potentially significant, auditory stimulus events in the environment (Todd *et al*. 2011, Näätänen *et al*. 2009, Shelley *et al*. 1991). The **P50** is elicited in a auditory dual-click or conditioning-testing task, where paired clicks are presented separated by an interval of 500 ms. The averaged ERP produces a response approximately 50 ms post stimulus, of positive polarity, the P50 wave. The relative decrease of the P50 wave to the second click (S2) compared with the first (S1), the S2/S1 ratio, has been used as a measure of **sensory gating**. This ratio is believed to reflect inhibitory mechanisms, an ability to inhibit intrinsic responses to redundant stimuli, that is impaired in schizophrenia (Patterson *et al*. 2008, Adler *et al*. 1982).

Arguably, attention and its key mechanism of salience detection (Corbetta and Shulman 2002), core elements of schizophrenia etiopathogenesis (Kapur 2003), modulate brain's reactions across the oddball task (Coull 1998), passive oddball (Todd *et al*. 2012) and gating paradigms (Rosburg *et al*. 2009, Potter *et al*. 2006). Those auditory ERPs represent different brain functions, which are **collectively** integrated in a multi-stage process involving bottom-up gestalt grouping primitives, auditory memory, attention and other forms of top-down control (e.g. motivational significance reflected in Error-

Related Negativity), that ultimately leads to the extraction of signal from noise and separation of foreground from background, in auditory scenes analysis (Fritz *et al*. 2007). Auditory attention theories underline brain's ability to engage in the processing of relevant stimuli, whilst simultaneously filtering out irrelevant stimuli and shift its focus following variations in the environment, sometimes alluded to as the "cocktail party" phenomenon (Shinn-Cunningham 2008, Fritz *et al*. 2007, Jaaskelainen *et al*. 2007). Perceptual objects compete for the attention focus, based on their inherent salience and the influence of top-down attention, the latter favouring objects with desired perceptual features (Shinn-Cunningham 2008, Fritz *et al*. 2007). Several mechanistic explanations for auditory attention have been put forward, including, at the auditory cortex level, center-excitation surround-inhibition, that is, the enhancement of neural sensitivity to some sound features with simultaneous inhibition of neural sensitivity to adjacent features (Jaaskelainen *et al*. 2007). At the neuronal level, stimulus-specific adaptation, the decline over time of neuronal responses to similar stimuli, may underlie auditory novelty detection (Ulanovsky *et al*. 2003).

1.3.1 Psychosis neurophysiological traits Vs progressive abnormalities

Each of the P300, MMN and P50 ERPs has been used according both to the neurodevelopmental and neurodegenerative conceptual approaches. One, looking at their quality as "trait" markers (in relation to psychosis genetic vulnerability, as an endophenotype) and the other as "state" markers (in relation to the clinical presentation of the illness, namely illness duration and symptoms severity).

Studies comparing **P300** amplitude at Pz in samples of healthy controls, prodromal, first episode and chronic schizophrenia patients (Van Tricht *et al*. 2011, Umbricht *et al*. 2006, Van der Stelt *et al.* 2005, Brown *et al*. 2002, Demiralp *et al*. 2002, Salisbury *et al*.

1998), together with family/twin schizophrenia studies (Groom *et al.* 2008, Hall *et al*. 2006, Price *et al*. 2006, Bramon *et al*. 2005, Winterer *et al*. 2003, Turetsky *et al*. 2000, Frangou *et al*. 1997), have found evidence for the trait hypothesis, however disease dependence (de Wilde *et al.* 2008) and progressive amplitude reduction have also been suggested by other studies (Chen *et al*. 2013, Ozgurdal *et al*. 2008, Martin-Loeches *et al*. 2001, Mathalon *et al*. 2000). Moreover, P300 amplitude has been shown to track the variation in severity of psychopathology (Turetsky *et al*. 2014, Mathalon *et al*. 2000). There are tentative associations between the P300 and candidate genes for psychosis, including DISC1 (Shaikh *et al*. 2013, Blackwood *et al*. 2001), Neuroregulin 1 (Bramon *et al*. 2008), however the case of the COMT Val158Met polymorphism illustrates the pitfalls in drawing conclusions about genetic associations between the P300, candidate genes and schizophrenia (Bramon *et al*. 2006).

MMN has been found associated to progressive brain abnormalities in schizophrenia (Jahshan *et al*. 2012, Magno *et al*. 2008, Umbricht *et al*. 2006, Brockhaus-Dumke *et al*. 2005), correlating in one study with left Heschl gyrus atrophy (Salisbury *et al*. 2007). A reduction in MMN amplitude was also found in adolescents from the general population (non clinical sample) with psychotic symptoms, a very early stage of risk (Murphy *et al*. 2013) and subjects with at-risk mental state (Higuchi *et al*. 2013, Hsieh *et al*. 2012). Most studies report little or no genetic influence on MMN (Magno *et al*. 2008, Hall *et al*. 2006, Price *et al*. 2006, Bramon *et al*. 2004), although the opposite has also been found (Michie *et al*. 2002). A MMN frontal amplitude reduction was associated with the presence of the COMT (108/158) Met allele on the single intact chromosome 22 of individuals with microdeletions at the chromosome 22q11.2, known to be at high risk for schizophrenia (Baker *et al*. 2005).

Brockhaus-Dumke *et al*. (2008) compared **P50** S2/S1 gating in samples of prodromals, first episode and chronic schizophrenia patients, who were all unmedicated, finding

reduced gating to be present already in the early stages of schizophrenia, however this deficit was more pronounced in chronic schizophrenia patients. This gradient was corroborated in another study including subjects in pre-psychotic state (Hsieh *et al*. 2012). There is evidence for a genetic link between the gating of the P50 ERP and schizophrenia (Hall *et al*. 2006, Price *et al*. 2006, Louchart-de la Chapelle *et al*. 2005, Clementz *et al*. 1998, Siegel *et al*. 1984), as well as bipolar disorder (Hall *et al*. 2008). A single nucleotide polymorphism in the 15q14 gene CHRNA7 5'core promoter has been associated with P50 suppression deficits (Freedman *et al*. 2003, Leonard *et al*. 2002). Methodological issues have however contributed to mixed findings with regards to the reliability of the P50 gating (Patterson *et al*. 2008) and its viability as an endophenotype (Light *et al*. 2012, De Wilde *et al*. 2007, Greenwood *et al*. 2007). N100 suppression in the same paradigm has been suggested as perhaps an alternative more robust measure (Brockhaus-Dumke *et al*. 2008, Turetsky *et al*. 2008).

In literature reviews (Javitt *et al*. 2008, Turetsky *et al*. 2007), P300 and P50 have been considered to exhibit deficits in both schizophrenia patients and unaffected family members, showing strong evidence of heritability, whereas MMN has stronger evidence as a state marker.

1.4 From ERPs to Event Related Oscillations (EROs)

In the last decade, brain oscillations in the EEG corresponding to patterns of brain rhythms (with different frequencies) have received great interest in a broad field of research and been shown to play a crucial role in neuronal synchronization, linking single-neuron activity to behaviour (Buzsaki and Draguhn 2004). Oscillations in the beta and gamma range establish synchronization with great precision in local cortical networks (Gray *et al*. 1989), whereas lower frequencies preferentially establish

synchronization over longer distances (von Stein *et al*. 2000). Event related brain oscillations (EROs) correspond to the changes in the frequency power spectrum of the ongoing EEG triggered by events and are correlated with different aspects of cognition including attention and memory (Başar and Güntekin 2008). Methods of spectral decomposition of the EEG, time-frequency analysis, are now well established, (Roach and Mathalon 2008) and time-frequency analysis provides information not only on the magnitude of the oscillations but also on their phase. The instantaneous phase of an oscillation refers to where a specific time point falls, within the cycle of the oscillation, it adds to the information from its spectral power, because it is independent of signal amplitudes. Intertrial coherence is a measure of phase locking for a single electrode, between time locked responses across trials (Delorme and Makeig 2004).

EROs can be further discriminated between two types: phase locked (evoked) or non phase locked (induced) to the eliciting event. The analysis of induced oscillations requires single-trial analysis whereas evoked oscillations can be obtained from the averaged ERP responses. This distinction provides additional information to the conventional time-voltage analysis of the ERP, which by averaging single trial EEG activity eliminates the non-stimulus-phase-locked activity. Broadly, induced oscillations are thought to reflect top-down brain activity, whereas evoked oscillations are thought to be stimulus driven and induced gamma band activity, in particular, has been implicated in several cognitive functions (Taullon-baudry 1996). Brain oscillations show cross-frequency coupling, which may serve as a mechanism to transfer information from large-scale brain networks operating at behavioral timescales to the fast, local cortical processing required for effective computation and synaptic modification, thus integrating functional systems across multiple spatiotemporal scales (Lisman and Jensen 2013, Canolty and Knight 2010). In a seminal study by Lakatos *et al*. (2008), during a visual attention task, delta phase was found to determine

power in higher-frequency (gamma) activity in the primary visual cortex and this coupling was inversely correlated with reaction times (Lakatos *et al*. 2008). Different methods have been proposed to measure this phenomenon, also referred to as nested oscillations (Penny *et al*. 2008, Cohen 2008, Jensen and Colgin 2007).

1.4.1 EEG time-frequency analysis in schizophrenia

EEG spectral abnormalities have consistently been found on the **resting EEG** in schizophrenia and a pattern profile of increased slow waves, decreased alpha and increased beta activity has emerged (Siekmaier and Stufflebeam 2010, Boutros *et al*. 2008). Schizophrenia patients' relatives also exhibit increased beta activity in resting state, suggesting excessive high-frequency EEG activity may serve as an endophenotype that reflects cortical expression of genetic vulnerability for schizophrenia (Narayanan *et al*. 2014, Venables *et al*. 2009).

The study of **Event related oscillations (EROs)** in schizophrenia and other psychiatric disorders has received increasing attention (Basar and Guntekin 2013, Moran and Hong 2011, Uhlhaas and Singer, 2010; Roach and Mathalon, 2008; Van der Stelt and Belger 2007). Literature findings on EROs associated to cognitive abnormalities in schizophrenia, for each of the commonly analyzed frequency bands, were summarized as follows by Ulhaas *et al*. (2008):

Table 1.3 | Summary of EROs abnormalities in schizophrenia

	Theta (4–7 Hz)	Alpha (8–12 Hz)	Beta (13–30 Hz)	Gamma (30–200 Hz)
Anatomy	Hippocampus, prefrontal cortex, sensory cortex	Thalamus, hippocampus, reticular formation, sensory cortex, motor cortex	All cortical structures, subthalamic nucleus, hippocampus, basal ganglia, olfactory bulb	All brain structures, retina, olfactory bulb
Neurotransmitters	GABA, glutamate, acetylcholine	Glutamate, acetylcholine, serotonin	Glutamate, GABA, dopamine	GABA, glutamate, acetylcholine
Function	Memory, synaptic plasticity, top-down control, long-range synchronization	Inhibition, attention, consciousness, top-down control, long-range synchronization	Sensory gating, attention, perception, motor control, long-range synchronization	Perception, attention, memory, consciousness, synaptic plasticity, motor control

The role of delta oscillatory responses in cognition and their impairment in different psychiatric disorders was not considered by Ulhaas *et al*. (2008), but reviewed more recently by Guntenkin and Başar (2015): these authors linked those brain oscillations to attentional and decision making processes and concluded that a deficit in delta oscillations may be a general electrophysiological marker for cognitive dysfunction.

Gamma oscillations have received particular attention, because of their putative role in higher cognitive processes such as object representation, attention and memory (Herrmann *et al*. 2010, Tallon-Baudry 2009). However, the ability to reliably measure this frequency band oscillations from the scalp EEG, due to the interference of microsaccades artifacts, has generated controversy (Yuval-Greenberg *et al*. 2008).

The current understanding is that different EROs time-frequencies reflect distinct brain functions and may be impaired by different disease mechanisms, moreover EROs interact across frequencies, therefore measuring and integrating multiple EROs is necessary in order to unravel schizophrenia complex neurophysiological abnormalities (Basar 2013, Moran and Hong 2011, Uhlhaas and Singer 2010, Roach and Mathalon 2008, Van der Stelt and Belger 2007).

Several studies have tried to make a **bridge between neurophysiological markers and clinical presentation** in schizophrenia. Positive psychosis symptoms were correlated with enhanced amplitude and phase synchronization of evoked and induced beta/gamma-band activity (Spencer *et al*. 2008, Lee *et al*. 2003), whereas negative symptoms were related to both enhanced (Spencer *et al*. 2004) and reduced high-frequency oscillations (Lee *et al*. 2003). EROs have also been associated to schizophrenia cognitive deficits. Patients showed reduced theta oscillations, involved in mediating frontal lobe activity and functions related to enhanced executive control, under varying working memory load (Schmiedt *et al*. 2005). Higher cognitive control demands were associated with increases in induced γ-band activity in the prefrontal areas of healthy subjects, but that control-related modulation of prefrontal γ-band activity was absent in schizophrenia subjects (Cho *et al*. 2006). Haenschel *et al*. 2009 found working memory deficits in schizophrenia patients to be associated with impaired oscillatory activity during all phases of the memory task and the cortical storage system in patients to reach its capacity limit at lower loads. Moreover, impaired cognitive control-related gamma cortical oscillatory activity was found to be present at the first psychotic episode in schizophrenia, and this was independent of medication status (Minzenberg *et al*. 2010).

Although the power and synchrony of specific neural oscillations are decreased in schizophrenia, evidence of greater high-frequency activity during the resting state, as well as during auditory and visual sensory processing in brain sensory areas of patients with hallucinations compared to those without (Spencer *et al*. 2008, Lee *et al*. 2003), suggests that the cortical areas involved in generating hallucinations might be hyperexcitable (Uhlhaas and Singer, 2010).

Several **neurotransmitter systems** that are abnormal in schizophrenia are also involved in the generation and synchronization of cortical oscillations. GABAergic inhibitory interneurons are of particular importance and have been proposed to have a role in entraining cortical pyramidal cells (Cobb *et al*. 1995). There is evidence that GABA neurotransmission is altered in schizophrenia, thus resulting in decreased strength of inhibitory connections, impairing neural synchrony and cognitive function (Gonzalez-Burgos and Lewis, 2008). Neural oscillations are also under glutamatergic control and the administration of ketamine to healthy subjects appeared to mimic some aspects of neural oscillatory deficits in schizophrenia, showing an opposite effect on scalp-recorded gamma *Vs* low-frequency oscillations (Hong *et al*. 2010). Dopamine is a neurotransmitter that has traditionally been implicated in the pathophysiology of schizophrenia. However, evidence for a direct impact of dopaminergic transmission on neural oscillations in schizophrenia is lacking. Nevertheless, dopamine (through dopamine D4 receptors) and Neuroregulin (NRG-1), which has been identified as a risk gene for schizophrenia, have been found to synergistically modulate gamma oscillations in the prefrontal cortex and hippocampus (Furth *et al*. 2013).

1.4.2 Oddball task, passive oddball and paired-click paradigms EROs in schizophrenia

In the **auditory oddball target detection paradigm**, used to elicit the P300 ERP component, schizophrenia patients show power reductions in delta and theta bands and this is associated with decreased P300 amplitude (Doege *et al*. 2009, Ford *et al*. 2008, Roeschke *et al*. 1997). Gamma synchrony was found to predict the P300 component in controls, but not schizophrenia patients (Ford *et al*. 2008). This disease was also

associated with impaired parietal event related alpha (Higashima *et al.* 2007) and beta (Fujimoto et al. 2012) attenuation in the auditory oddball task.

In the **passive oddball paradigm**, dependence of MMN amplitude on theta band oscillations has been shown in healthy subjects (Fuentemilla *et al*. 2008). Slow waves power in the resting EEG of schizophrenia patients was inversely correlated to MMN (Kirino and Inoue 1999) and MMN theta-alpha range oscillations were abnormally enhanced in schizophrenia patients (Hong *et al*. 2012).

In the **paired-click paradigm**, schizophrenia patients show reduced gating of the theta/alpha frequency bands (Hong *et al*. 2008), EROs that contribute to the P50 component amplitude (Brockhaus-Dumke *et al*. 2008, Jansen *et al*. 2004). Others have found abnormalities in faster, beta/gamma (Brenner *et al*. 2009, Hong *et al*. 2004, Clementz *et al*. 1997) EROs. Phase synchronization (2-12Hz range) deficits, in response to the conditioning stimulus and impaired correlation between phase synchronization and the N100 were also described (Jansen *et al*. 2004). Of note, ERPs may arise both by amplitude modulation and/or phase resetting of ongoing brain oscillations, in different frequency bands, however the proportion of the contribution of each of the two mechanisms is generally not entirely clear (Sauseng *et al*. 2007).

Some studies have looked at the suitability of brain **EROs as schizophrenia endophenotypes**, with encouraging results. The early auditory evoked gamma-band response (Hall *et al*. 2011, Leicht *et al*. 2011, Leicth *et al*. 2010) and theta-alpha frequency EROs gating (Hong *et al*. 2008) were found abnormal both in schizophrenia patients and in their first-degree relatives. Few studies have yet looked at the associations between EROs and psychosis candidate genes in clinical samples of patients. One study found no association between noise power in the gamma band and Neuregulin gene variants (Diez *et al.* 2014). In healthy subjects, a modulation of evoked

gamma activity, during an auditory target detection paradigm, by DRD4 and DAT1 polymorphisms, but not by COMT polymorphisms, has been described (Furth *et al*. 2013, Demiralp *et al*. 2007). Of note, the same polymorphisms had no influence on P50, N100, or P300 amplitudes or latencies (Demiralp *et al*. 2007).

1.5 Combining neurophysiological paradigms to characterize psychosis

It has can be argued that combining different neurophysiological paradigms on the same sample of patients is potentially advantageous because they can complement each other and characterize the population more accurately (Turetsky *et al*. 2009, Price *et al*. 2006). There have also been reports of associations between MMN-P300 (Gjini *et al*. 2010, Leitman *et al*. 2010) and P50 gating-MMN (Gjini *et al*. 2010, Kisley *et al*. 2004) deficits in schizophrenia. A combined ERP study on schizophrenia twins, allowed to compare the genetic correlations between P300, P50 ratio, MMN and phenotypical disease expression (Hall *et al*. 2006). Although the 3 auditory paradigms have different theoretical underpinnings and are likely to tap onto different neurobiological mechanisms, combined they could better capture the polygenic nature of psychotic illnesses and increase diagnostic sensitivity and specificity. By being relatively independent, they may help to unravel the heterogeneity of physiopathological mechanisms, deficits, genetic and non genetic pathways in schizophrenia.

1.6 Aims and hypothesis

Overall, there is strong evidence to suggest that oscillatory brain activity underlies perceptual and cognitive processes, which are themselves affected in psychosis. Event related brain oscillations may complement conventional ERPs in measuring abnormal brain dynamics. Because EROs can be quantified reliably, they may become valuable diagnostic markers, endophenotypes for genetic studies, an aid to staging disease and/or guiding treatment.

Hence, the object of my study is the broad band spectral EEG power, extracted from the brain responses in the auditory oddball task, passive oddball and paired-click paradigms. Three main hypothesis are tested:

1. Psychosis patients exhibit deficits in auditory attention-related EROs when compared to controls;
2. First-degree relatives of psychosis patients show abnormal auditory attention-related EROs when compared to controls, indicating that these EROs are markers of genetic vulnerability to psychosis;
3. There is an increasing gradient in the magnitude of auditory attention-related EROs abnormalities, indicating progression of disease from ARMS subjects, through early psychosis patients to chronic patients.

Chapter Two – Methodology

2.1 Study Sample

The overall study sample, outlined in Table 2.1a, contains 35 patients with early psychosis, 44 patients with chronic psychosis, 69 unaffected first-degree relatives, 40 ARMS individuals and 76 unrelated controls with no history of psychosis. From this sample, I selected sub-samples for analysis, based on the availability of the EEG data. An overview of this process and the various samples investigated in the course of this thesis is presented in Figure 2.1a.

The vast majority of patients included in this study had schizophrenia, schizoaffective disorder or another psychotic disorder (Table 2.1a), however a small number of bipolar disorder patients were also included, if the patient had a lifetime DSM-IV diagnosis of bipolar affective disorder type-1 with clear psychotic features (experiencing hallucinations and/or delusions at some point during their symptom exacerbation). All but 6 psychosis patients were medicated, the majority with an antipsychotic or a combination of antipsychotic + mood stabilizer/antidepressant (Figure 2.1b).

Most participants (controls, ARMS and early psychosis patients) were recruited individually, but part of the chronic patients and relatives groups were recruited as part of a family study. Of the 264 participants, 181 (68.56%) were singletons, 58 (21.97%) were part of families with two members in the study, 21 (0.08%) were in three-person families, and 4 (0.015%) were part of one family with four members participating.

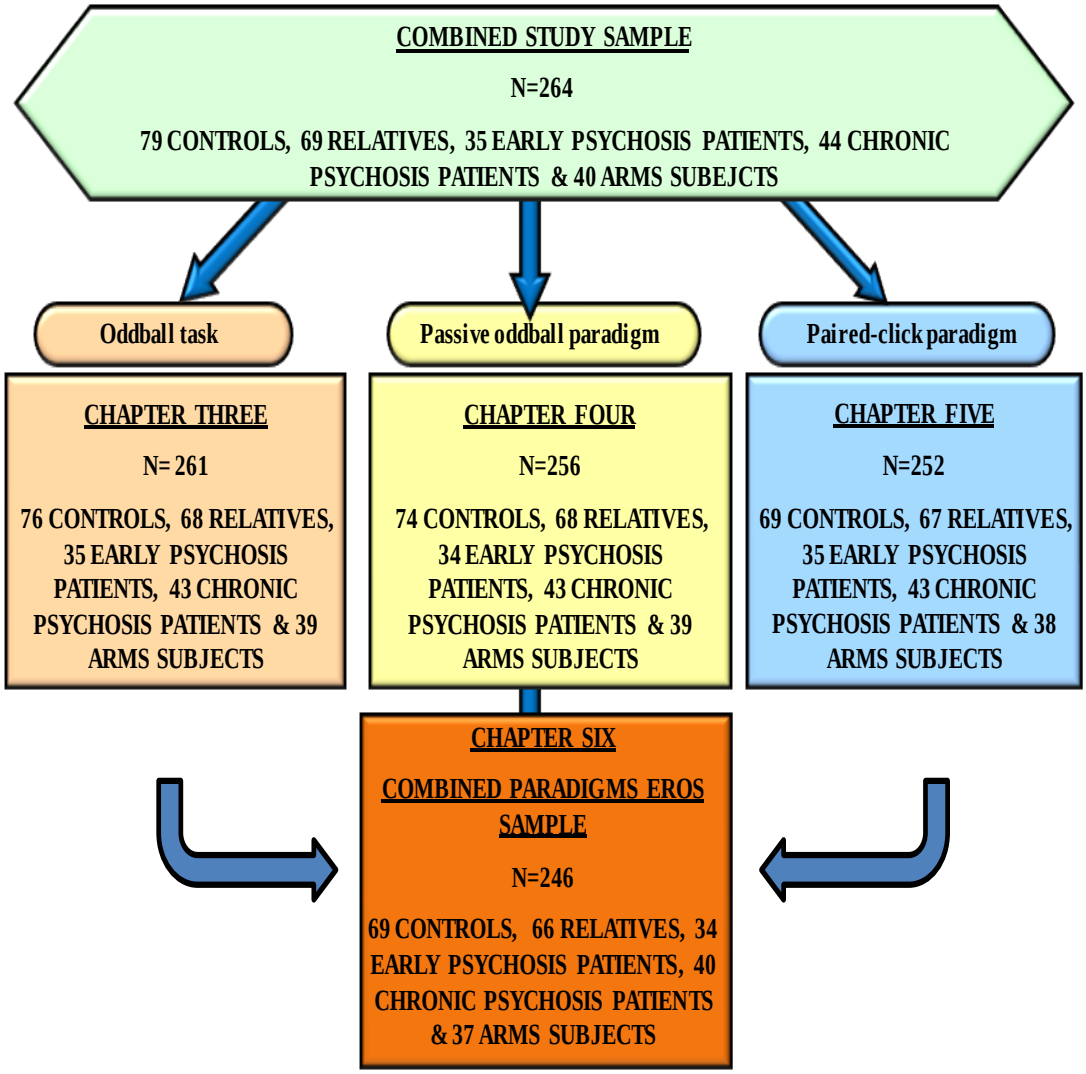


Figure 2.1a Breakdown of samples under investigation

Table 2.1a | Clinical and demographic characteristics of overall sample

Group		Controls	First-degree relatives	Psychosis patients	ARMS	
N		76	69	79	40	
♀ : ♂ (% Male)[a]		34 : 35 (51%)	41 : 28 (41%)	20 : 59 (75%)**	16 : 24 (60%)	χ^2 (3) = 18.1, p<0.001
Mean Age (SD)[b]		34.6 (14.0)	52.0 (15.8) ***	34.1 (12.1)	24.2 (4.2) **	F (3,252) = 40.4, p<0.001
Tobacco[2] – Non-Smokers : Smokers (% Smokers)[c]		66 : 10 (13%)	49 : 18 (27%)*	27 : 51 (65%)***	11 : 18 (62%)***	χ^2 (3) = 54.9, p<0.001
DSM-IV Diagnosis		No Psychiatric Disorder (73) Major depression (1) Minor depression (2)	No Psychiatric Disorder (42) Major depression without psychotic features (21) Anxiety disorder (4) Cyclotymic disorder (1)	Schizophrenia (57) Schizoaffective Disorder (7) Bipolar Disorder, type 1 (7) Schizophreniform Disorder (3) Acute and transient psychotic disorder (3) Major depressive disorder, with psychotic symptoms (1)	No Psychiatric Disorder (12) Depressive disorder (6) Substance misuse (5) Anxiety disorder (3) Personality disorder (2) Personality disorder and depression (2)	
Positive And Negative Symptoms Scale[3]	**Positive (SD)**	-	-	11.2 (4.4)		
	Negative (SD)	-	-	16.5 (8.1)		
	General (SD)	-	-	27.8 (8.5)		
	Total (SD)	-	-	55.6 (18.0)		

[a] Significant gender differences were found between the study groups: the psychosis patients group had more males than the controls group. [b] There were significant age differences between the study groups: relatives were older and ARMS subjects were younger than controls. [c] There were smoking status differences between the study groups: first-degree relatives, psychosis patients and ARMS subjects groups included more smokers than the controls group. *,** and *** indicate significant differences from control group at $p<0.05$, $p<0.01$, $p<0.001$ respectively.

Table 2.1b | Breakdown of clinical and demographic characteristics of psychosis patients

Group		Early psychosis patients	Chronic psychosis patients	
N		35	44	
♀ : ♂ (% Male)		9 : 26 (74%)	11 : 33 (75%)	n.s
Mean Age (SD)		24.9 (4.1)	41.4 (11.3) ***	t (77) = 8.2, p<0.001
Tobacco[2] – Non-Smokers : Smokers (% Smokers)		9 : 25 (74%)	18 : 25 (59%)	n.s.
Mean Age at onset in years (SD)		23.0 (4.4)	-	
Mean Duration of illness in months (SD)		23.3 (15.2)	-	
Mean Number of hospitalizations (SD)		1.3 (0.9)	-	
DSM-IV Diagnosis (n)		Schizophrenia (22) Bipolar Disorder, type 1 (5) Schizophreniform Disorder (3) Acute and transient psychotic disorder (3) Schizoaffective Disorder (1) Major depressive disorder, with psychotic symptoms (1)	Schizophrenia (35) Schizoaffective Disorder (6) Bipolar Disorder, type 1 (2)	
Positive And Negative Symptoms Scale[3]	**Positive (SD)**	10.3 (3.9)	12.1 (4.7) *	t (68) = -2.1, p = 0.04
	Negative (SD)	18.2 (8.3)	15.0 (7.6)	n.s
	General (SD)	29.3 (8.2)	26.5 (8.6)	n.s
	Total (SD)	57.8 (17.8)	53.9 (18.1)	n.s

No data was available for the chronic patients sample on age at onset, duration of illness, nor number of hospitalizations. PANSS data was available for 33 early psychosis patients and 37 chronic psychosis patients. * and *** indicate significant differences from the early psychosis group at $p<0.05$ and $p<0.001$ respectively. **n.s** indicates statistically non significant. Group compasisons here are unajusted for multiple comparisons.

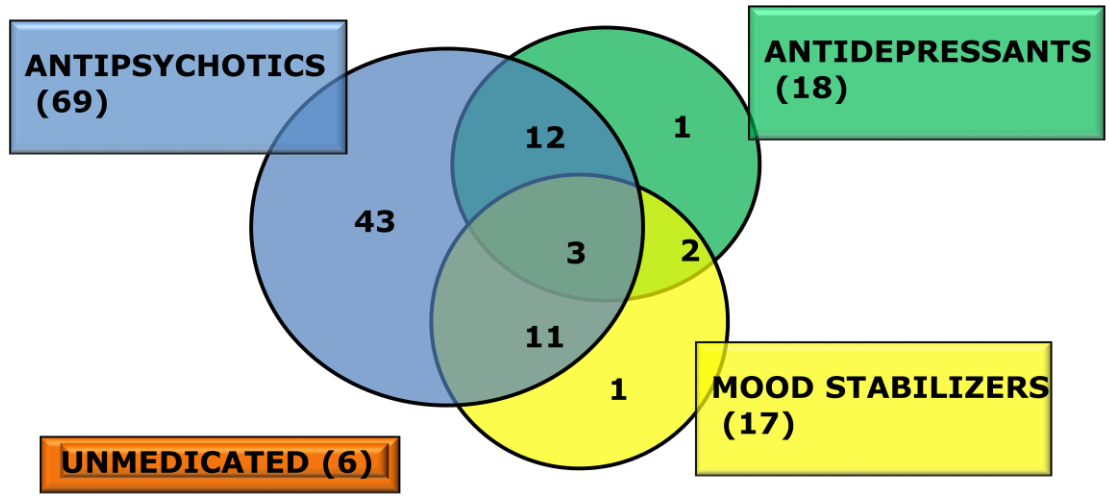


Figure 2.1b Patients group medication profile

2.2 Recruitment of early psychosis patients

Patients were eligible to enter this group if they were aged between 18-35 years old, had a DSM-IV diagnosis of a psychotic disorder (table 2.1a), an onset of psychotic symptoms less than 5 years previously and were able and willing to give informed consent in order to enter the study. They were recruited from the Lambeth early onset (LEO) service at the South London and Maudsley NHS Foundation Trust, both from the inpatient unit and community team.

2.3 Recruitment of chronic patients and their first-degree relatives

Families with one or more affected member were recruited by direct contact with mental health charities such as Rethink (formerly the National Schizophrenia Fellowship) and MIND (The National Association for Mental Health), and a wide variety of mental health service user groups across Greater London. Advertisements in the form of posters or short articles were also placed in the newsletters of these groups,

posted on a number of online forums for people with mental health issues and displayed inside a number of mental health care units. Patients selection criteria in this group differed from the early psychosis sample in that there was no maximum age limit and there was a minimum 5 years' duration of illness.

2.4 Recruitment of ARMS subjects

The 40 individuals of the ARMS psychosis group had an 'at risk mental state' (ARMS) according to criteria established by Yung and colleagues. This includes people with sub-clinical 'attenuated' psychotic experiences, individuals with psychotic symptoms of insufficient duration to reach a diagnosis ('brief limited intermittent psychotic symptoms' known as BLIPS), subjects with schizotypal personality disorder, or those with a first-degree relative with psychosis and who are experiencing a significant decline in function (Yung *et al.* 2005). ARMS subjects were recruited through the clinical service "Out-reach and Support In South London" (OASIS). None of the ARMS were taking antipsychotics at the time of EEG testing and the majority were antipsychotic naive.

2.5 Recruitment of healthy controls

Healthy controls were recruited from the community via advertisements in the local press (The Evening Standard, South London Press and The Metro) and through the newly created MindSearch database of controls at the Institute of Psychiatry. All volunteers for the study were compensated for their travel expenses and for their time spent undertaking the study. Participants gave written informed consent to enter the study. My research was approved by the Institute of Psychiatry Ethical Committee

(study references 038/00, 285/01, 011/99) and the Multi-Centre Research Ethics Committee (MREC reference 01/06/06).

2.6 Study inclusion and exclusion criteria

Participants were of mixed ethnic backgrounds, including caucasian and black ethnicity. Exclusion criteria were the presence of a neurological disorder or organic brain disease, head injury that resulted in loss of consciousness for a period longer than 10 minutes, or a DSM-IV diagnosis of alcohol or substance dependence in the 12 months prior to participation. Patients had a DSM-IV diagnosis of a psychotic disorder or mood disorder with psychotic symptoms. Controls had no personal or family history of psychosis, including schizophrenia, schizoaffective or bipolar disorders. History of a non-psychotic psychiatric disorder such as depression was not an exclusion factor, provided controls or 1st-degree relatives had recovered and not taken any psychotropic medication during the prior 12 months.

2.7 Clinical and socio-demographic Assessments

2.7.1 Screening

All participants were screened using a telephone interview to ensure they met the criteria for the study before being invited to attend. Details of the study and what they were to expect during their visit were given orally to the individual or key family member. These were also provided again in printed form along with a letter confirming their appointment. Copies of all information given to the participants and the questionnaires they were required to complete can be found in appendix one.

2.7.2 Clinical assessments

All new participants underwent a clinical assessment by a psychiatrist (Dr Elvira Bramon, Dr Miguel Constante or Dr Anirban Dutt). A structured diagnostic interview using the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) (Endicott and Spitzer 1978) was completed to enable a DSM-IV diagnosis to be reached. Medical records were consulted where available if any uncertainty remained concerning diagnosis. The Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987) was also completed by the clinician during the assessment.

2.7.3 Family history

The Family Interview for Genetic Studies (FIGS) (Nurnberger *et al.* 1994) was used to assess family history of mental illness and acquire information on family members not available for interview. The unaffected mother or father was the primary informant for a family and controls reported their own family history.

2.7.4 Further assessments

Information on handedness, educational history, and current nicotine, alcohol and illicit drug use was collected verbally at initial screening interview and on day of participation by both interview and questionnaire.

2.8 Recording of EEG

New recordings undertaken as part of my data collection were carried out at the Neurophysiology Laboratory in the Psychosis Centre of the Institute of Psychiatry, King's College London. Previously recordings by my colleagues were carried out either

in the same lab, or at the Electrophysiology Laboratory inside The Eric Byers Magnetic Resonance Suite of Mapother House. As part of the research protocol, subjects were always requested not to smoke at least 30 minutes before data collection (Adler *et al*., 1993). EEG data was recorded using a 40-channel Quik-Cap electrode cap positioned according to the 10/20 International System as shown in Figure 2.8a, referenced to linked mastoids and grounded at Fpz, a SCAN NuAmps Express^{TM} 40-channel monopolar digital amplifier and SCAN software package version 4.3 (Compumedics Neuroscan, Texas, USA). Eye movements and blinking were recorded from electro-oculogram (EOG) electrodes activity placed at four electrodes performing vertical and horizontal EOG recording in bipolar montage, as shown in Figure 2.8b. To prepare these areas and the mastoids before the placement of electrodes, abrasive gel was gently applied to the skin *(NuPrep Abrasive Skin Prepping Gel, D.O Weaver and Co. Colorado, USA)*, and this was then cleansed with an alcohol swab *(70% Isopropyl Alcohol Alcotip Swab, Universal Hospital Supplies Ltd., UK)*. This process reduces the impedance between the surface of the skin and the conductive gel by removing makeup, skin oil and dead skin cells. Electrode impedances were below 5 kΩ. Data was continuously digitised at 1000 Hz with a digital 0.1-100 Hz band pass filter (24 dB/octave roll-off).

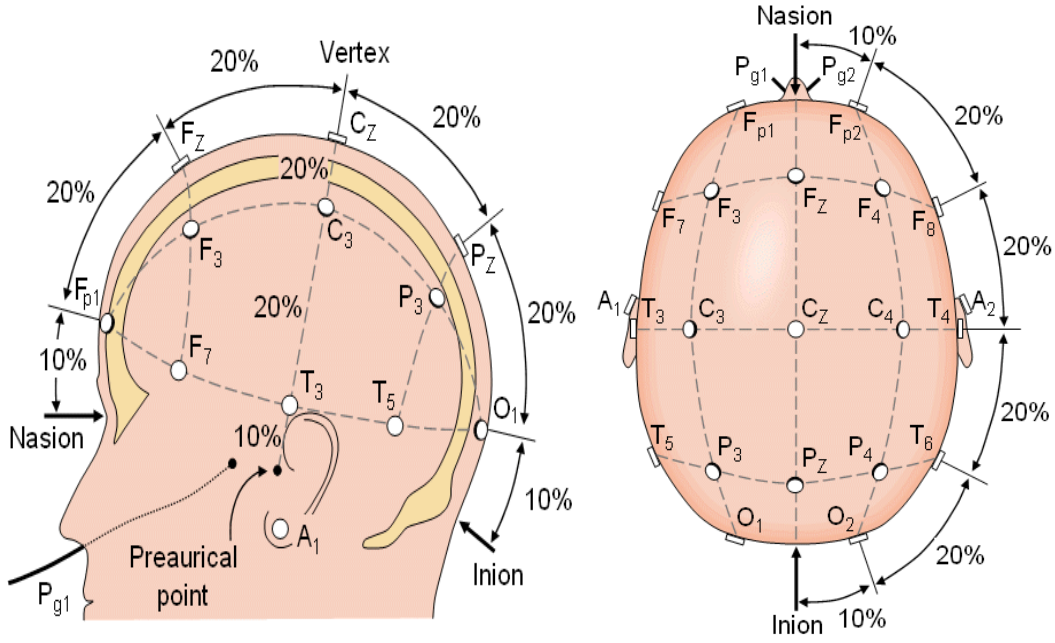


Figure 2.8a The 10/20 International System for electrode placement

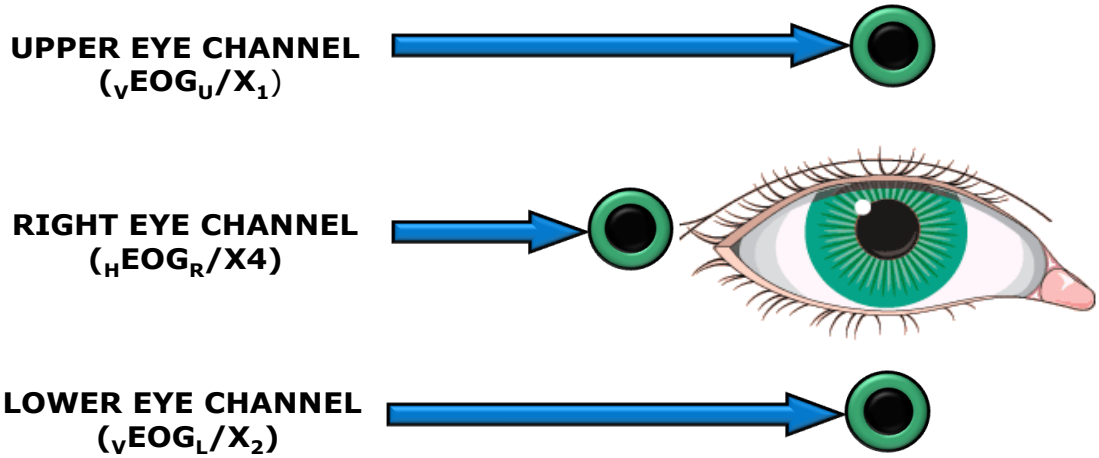


Figure 2.8b Placement of electro-oculogram (EOG) electrodes at right eye

Stimuli were generated and presented using the STIM stimulus presentation system *(Compumedics Neuroscan, Texas, USA)* and delivered though intra-aural earphones *(ER3-14A Eartips for ER-3 and ER-5, Etymotic Research Inc. Illinois, USA)*. Each recording session lasted approximately 45 minutes and the neurophysiological paradigms detailed below were carried out in this order: 1st - paired-clicks, 2nd auditory oddball task and 3rd. passive oddball (these were followed by recording of the resting EEG and PPI paradigm, which were not subject of study in this thesis). Participants

were seated in a comfortable chair, requested to fixate a point on the desk in front and keep their eyes open throughout the testing. While the equipment used in the acquisition of the EEG data had minor changes between the two laboratories used, the stimulation paradigms remained the same. A detailed description of the specifics of the different laboratories and the changes in data collection methodology is contained in appendix two.

2.9 Oddball task paradigm

The auditory oddball task (Bramon *et al.* 2005; Schulze *et al.* 2008) consisted of one block of four hundred 80 dB, 20-msec tones, with a 2 second (±0.2 second) inter-stimulus interval presented through bilateral intra-aural earphones. 80% of the tones were 'non-targets' of 1000 Hz and 20% were 'targets' of 1500 Hz, in a random sequence. Subjects were instructed to press a button with their preferred hand in response to target tones only. Reaction time (RT) was measured as the button press median response latency to target tones, in milliseconds. Only trials with correctly identified target tones were used for later EROs/ERPs analysis.

2.10 Passive oddball paradigm

The passive oddball paradigm consisted of three blocks of 400 binaural 80-dB stimuli (0.3 sec inter-stimulus interval) per block, with 85% standards (1000 Hz, 25 ms, 5-ms rise/fall time) and 15% duration deviants (1000 Hz, 50 ms duration, 5 ms rise/fall time) (Bramon *et al.* 2004). Subjects were instructed to remain still and quiet throughout the test, to keep their eyes open and disregard the sounds presented to them.

2.11 Paired-click paradigm

The paired-click paradigm consisted of four or five blocks of 30 pairs of conditioning (S1) and test (S2) clicks (Schulze *et al.* 2007; Hall *et al.* 2008). S1 and S2 clicks were of 1 ms duration and separated by 500 ms. Intertrial intervals between click pairs were 10 seconds. Subjects were instructed to avoid blinking during the click presentations. Stimulus intensity was adjusted individually to 43 dB above the subject's hearing threshold.

2.12 Common EEG preprocessing to all paradigms

Data analysis was performed offline using the Matlab-based FieldTrip toolbox (http://fieldtrip.fcdonders.nl/). Before time-frequency or ERP analysis, the continuous EEG was segmented into large epochs (–3100 to 2500 ms) in order to allow measurement of low frequency EROs in the observation intervals and minimize edge effects. Artefact rejection was performed to exclude data segments containing eye blinks, muscle artefacts and amplitudes exceeding +/- 100 μV. Line noise removal was performed at 50Hz using a discrete Fourier transform. These artefact-free epochs were then used in two different processing pipelines, for the purpose of either time-frequency or ERP analysis, as detailed below.

2.13 ERP analyses methods

For the purpose of P300 ERP analysis, the EEG was digitally filtered (0.05–40 Hz) and epochs were baseline corrected (–200 to 0 ms), averaged to yield the target ERP

waveforms. P300 amplitude was measured at Pz, using a computer algorithm to calculate peak (between 250 to 450ms) to baseline difference. P300 latency was measured as the post-stimulus latency to P300 peak, in milliseconds.

For the purpose of MMN ERP analysis, the EEG data was filtered (0.03–40 Hz), and baseline corrected (–50 to 0 ms). MMN was extracted by subtracting the averaged waveforms for the standard stimuli from those for the deviant stimuli. The amplitude of the Mismatch Negativity waveform was measured at Fz, calculating the difference between mean MMN (130 to 190ms) and MMN baseline (-50 to 0ms), using a computer algorithm.

For the purpose of P50 ERP analysis, the EEG signal was filtered (10Hz high-pass filter), and corrected for baseline values (–50 to 0 ms). Epochs were averaged separately for the S1 and S2. P50 peak amplitudes for S1 and S2 were measured at the Cz site, in the 50–70ms post-stimulus interval, using a computer algorithm based on previous studies (Olincy *et al.* 2010, Nagamoto *et al.* 1989): S2 P50 latency had to be a value within ± 10 ms of S1 P50 latency; P50 amplitude was measured relative to its preceding trough; S1 P50 waves with less than 0.5 μV were excluded. P50 ratio was calculated as S2/S1 P50.

2.14 Time-frequency analyses methods

Time-frequency analyses were performed using the 'wavelet method', based on Morlet wavelets with a 'width' of 4 (Roach and Mathalon, 2008; Başar *et al.* 2001). In each studied paradigm, power was extracted with a 1 Hz (frequency) and 1 msec (time) resolution, from single trials, using artefact-free data segments following the initial EEG processing routine described above. The time-frequency transformation was applied to the baseline and post-stimuli intervals. The EEG frequency bands of interest were Delta

(1-3Hz), Theta (4-7Hz), Alpha (8-12Hz), Beta (13-30Hz) and Gamma (31-100Hz). Power values were calculated in microV2, then for EROs calculation, relative baseline correction (the quotient of post stimuli power over baseline average power) was applied. Baseline lengths were determined separately for each band: Delta (-1000 to 0 ms), Theta (-250 to 0 ms), Alpha (-125 to 0 ms), Beta (-100 to 0 ms), Gamma (-50 to 0 ms). Hence, EROs presented in time-frequency spectrums in this thesis results chapters represent the relative change of spectral power in comparison to the baseline: $\frac{\text{Post stimuli power}}{\text{Mean power in baseline interval}}$. EROs of interest were considered to be those with a functional association, that is, linked to either: a) task (condition) effects; b) behavioural performance, as measured by oddball task reaction time; c) psychosis symptoms; or that would d) discriminate between patients and controls. To identify these EROs, t-test comparisons were performed between each paradigm's two stimuli EROs time-frequency spectrums (target Vs non-target conditions, deviant Vs standard stimuli, S1 Vs S2 clicks), between groups (controls Vs patients) and EROs time-frequency spectrums were regressed with reaction time and PANSS scores. This resulted in time-frequency maps with clusters of statistically significant t-test scores and regression coefficients (Gross, 2014). These clusters were mapped onto target tone, deviant tone and S2/S1 EROs time-frequency spectrums, to delimitate EROs of interest. Task and reaction time effects on EROs were studied in patients and controls groups separately, to characterize disease effects, but also in the whole sample, the latter to maximize statistical power. The above method identifies specific EROs time-frequency clusters, where: a) the task effect is linked to either an attenuation or an increase in EROs between the two conditions; EROs have either a direct or an inverse relationship with b) processing speed (i.e., RT) and c) psychosis symptoms severity; d) patients show EROs deficits. Finally, composite EROs ratios combining EROs across frequencies were calculated, following the same rational as others have used in various studies

investigating EEG markers of attention and cognition (Schleiger *et al.* 2014, Sangal and Sangal 2014, Putman *et al.* 2014, Moretti *et al.* 2014, Staikou *et al.* 2012, Ogrim *et al.* 2012, Leon-Carrion *et al.* 2009, Barry *et al.* 2009).

EROs of interest, as defined above, were combined in composite EROs measures in order to reflect psychosis impairments in: 1) Isolated EROs time-frequency clusters; 2) EROs "collective behaviour", as ensembles of EROs time-frequency clusters that are functionally linked in each studied paradigm. This approach allows to establish functional links between different EROs, within and across the three studied paradigms and thus integrate different brain processes, as argued by various authors (Basar 2013, Buzsáki and Watson 2012, Moran and Hong 2011, Uhlhaas and Singer 2010). Although this overall method and rational was applied equally to the three studied paradigms, the specific time-frequency EROs clusters extracted from each and used in hypothesis testing are described in the respective results chapter (chapters 3 to 5).

2.15 Statistical Analysis

EROs time-frequency spectrums differences between conditions and groups, as well as the association between EROs and oddball task reaction time/psychosis symptoms, were analyzed and adjusted for multiple comparisons by means of a cluster based test statistic (for temporal and spectral adjacency) using a dependent/independent samples t-test or linear regression as appropriate and a threshold alpha=0.05; Monte Carlo significance probability was calculated using 1000 random partitions, the maximum of the cluster-level summed t-values and a cluster threshold alpha=0.05 (Maris and Oostenveld, 2007).

Group differences for reaction time, extracted EROs, P300, MMN and P50 gating measures were tested by ANOVA models, including as covariates age, gender, lab and

smoking (smoker Vs non-smoker) status. An overall test of significance was followed up by multiple pairwise comparisons, correcting for experiment-wise error rate by means of the tukey-kramer test. Another ANOVA model with an interaction term: clinical group * $\left(\frac{\text{Passive oddball EROs}}{\text{Paired−click paradigm EROs}}\right)$, as independent variable and oddball task EROs as dependent variable, was used to test the relationship between lower level and higher level EROs across the study groups. $\frac{\text{Passive oddball EROs}}{\text{Paired−click paradigm EROs}}$ fraction increases in value when both salience **and** gating brain functions are stronger. The hypothesis here is that psychosis impairments in basic sensory processing (salience and gating mechanisms) converge and feed into higher-order cognitive (selective attention) impairment (Dias *et al.* 2011, Leitman *et al.* 2010, Gjini *et al.* 2010), in this way testing relationships between the studied paradigms EROs. The three paradigms EROs were introduced together in regression analysis to predict PANSS positive and negative symptoms scores.

CHAPTER THREE

ODDBALL TASK EROS IN PSYCHOSIS

3.0 Introduction

In this chapter, abnormalities in the oddball task event-related measures are evaluated as to markers of genetic liability (and potential as psychosis endophenotypes) and also markers of psychosis chronicity. The sample recruitment, EEG data collection and statistical analysis methodologies which contributed to the following analyses are those outlined previously in chapter two. The following is examined in order to first identify relevant oddball task EROs and understand their dynamics: 1) the EROs condition effect, that is, the difference between oddball task target tone and non-target tone EROs responses, which should reveal EROs markers of selective attention resources allocation to stimulus processing. 2) the EROs association with reaction time, linking brain activity with a behavioural response that is indicative of brain processing speed. 3) the EROs association with psychosis symptoms as measured by PANSS total scores. 4) the EROs group effect, that is, controls Vs patients between-group comparisons of oddball task target and non-target tones EROs. EROs statistically associated to the above effects are considered relevant, thus extracted for hypothesis testing.

As per the study aims, the main hypotheses here are that: psychosis patients show disease associated oddball task EROs deficits, when compared to controls; psychosis genetic liability will manifest as first-degree relatives' intermediate deficits in oddball task EROs, between patients and healthy subjects; increasing oddball task EROs

deficits, starting from ARMS, through early psychosis patients to chronic psychosis patients will reflect disease progression.

P300 ERP results, although not the main focus of attention in this study, are presented here because they are in themselves of interest, as per the large amount of published research on the P300 in psychosis, including by our group. Moreover, they help to validate and interpret overall findings.

3.1 Between-group comparisons of P300 amplitude and reaction time

Mean P300 ERP amplitude and latency, reaction time (RT) by clinical group and the results of the ANOVA P300 amplitude group comparisons are shown in Tables 3.1a and 3.1b. There was no significant effect of group on P300 amplitude, after adjustment for a significant gender effect, $F(1,252) = 7.25$, $p=0.008$, where women showed larger P300 amplitude than men ($\Delta = 1.81\mu V$, 95% CI= 0.49 to 3.13μV). Age, smoking and lab had no effect on P300 amplitude. P300 latency increased with age, $F(1,252) = 43.22$, $p=2.85e^{-10}$, $\beta=0.87$, but there were no significant group, lab, smoking, nor gender effects. Estimated mean reaction time (RT) by clinical group is shown in Table 3.1a and Figure 3.1b. RT showed a significant main effect for group ($F(4,260) = 6.83$, $p<0.0001$), where controls showed faster RT than early psychosis patients (Δ = -117ms, 95% CI = -182 to -52ms) and chronic psychosis patients (Δ = -68ms, 95% CI = -129 to -7ms). All other group comparisons showed no statistically significant difference in RT. There was a gender main effect on RT ($F(1,260) = 12.24$, $p<0.001$), men were on average faster than women (Δ = -49ms, 95% CI= -78 to -19ms). There was a significant group * age interaction effect, $F(1,236) = 5.21$, $p<0.001$, where RT was slower with advancing age in chronic patients ($\beta=3.58$, $p=0.03$), but faster with advancing age in early psychosis ($\beta=-11.98$, $p=0.01$) and ARMS ($\beta=-13.22$, $p=0.01$) subjects. There was no significant lab effect.

P300 amplitude, P300 latency and reaction time (RT)

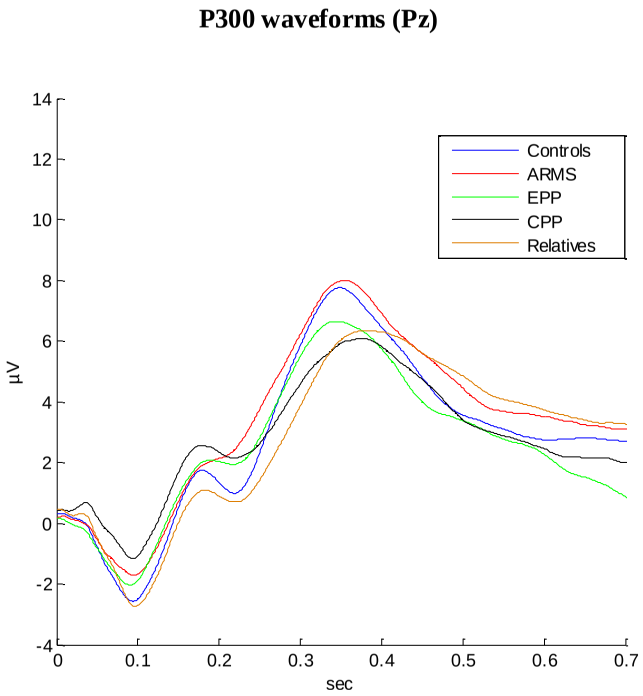


Figure 3.1a P300 grand average waveforms for all study groups, unadjusted for age nor gender effects. Amplitude (microV) is plotted over time (seconds). Time zero denotes the occurrence of stimuli. Waveforms have been smoothed and the peak of the grand average waveforms does not coincide with the mean of the individual P300 peak amplitudes presented in table 3.1a.

Table 3.1a | P300 amplitude, P300 latency and reaction time (RT)

	P300 amplitude (μV)	P300 latency (ms)	Reaction time (ms)
Controls	10.01 (0.61)	334 (3.96)	401 (13)
EPP	9.22 (0.92)	337 (6.20)	519 (20)
CPP	9.92 (0.86)	337 (5.23)	469 (18)
ARMS	8.92 (0.86)	333 (6.77)	445 (19)
Relatives	9.08 (0.65)	326 (4.85)	426 (14)

Mean (standard error) P300 amplitude, P300 latency at Pz electrode and reaction time (RT) for each study group. P300 amplitude is adjusted for gender, P300 latency is adjusted for age and RT is adjusted for gender.

Table 3.1b: P300 amplitude between-group comparisons

	Est. Mean Difference	95% CI	*F* (df) P Value
1. Controls Vs EPP	0.83	-2.19 to 3.85	
2. Controls Vs CPP	0.14	-2.75 to 3.02	
3. Controls Vs ARMS	1.14	-1.75 to 4.03	**0.51**
4. Controls Vs Relatives	0.98	-1.48 to 3.43	**(4,252)**
5. EPP Vs CPP	-0.70	-4.09 to 2.69	**p=0.73**
6. EPP Vs ARMS	0.31	-3.11 to 3.72	
7. EPP Vs Relatives	0.14	-2.97 to -3.26	
8. CPP Vs ARMS	1.00	-2.30 to 4.31	
9. CPP Vs Relatives	0.84	-2.15 to 3.83	
10. ARMS Vs Relatives	-0.16	-3.14 to 2.81	

P300 amplitude estimated mean differences between the study groups and 95% confidence intervals, adjusted for multiple comparisons.

Reaction time (RT)

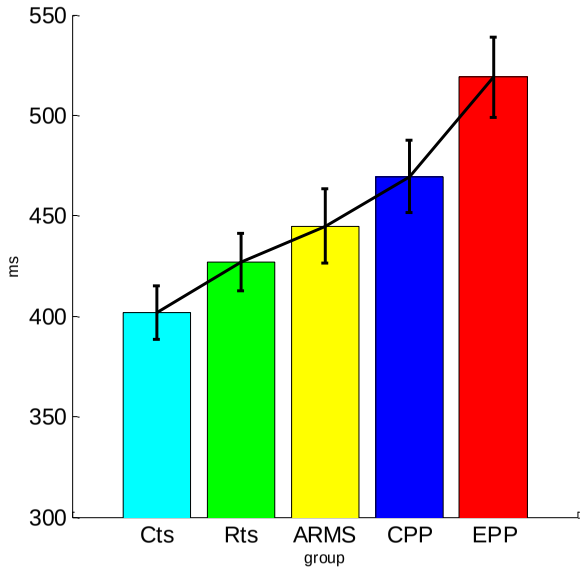


Figure 3.1b Reaction time (ms) for the study groups, adjusted for gender.

Cts - controls; Rts - first-degree relatives; EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

3.2 Oddball task EROs time-frequency plots

Oddball task paradigm EROs time-frequency plots for both target and non-target tone, by study group, are displayed in Figure 3.2.

Oddball task EROs time-frequency plots by condition and study group

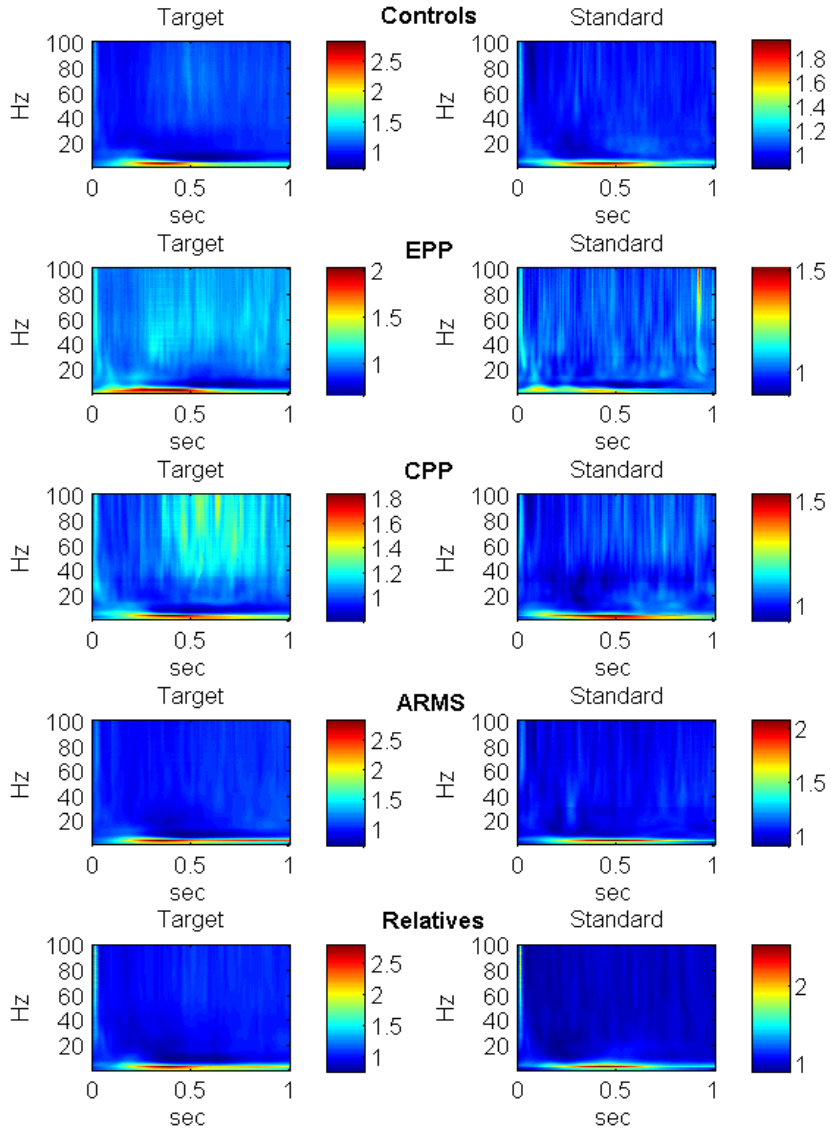


Figure 3.2 The EROs time-frequency plots depict mean change in power, in relation to the prestimulus baseline, for target (left) and non-target (right) tones and for each study group (different rows). EEG frequency is indicated on the y-axis of each plot and spans 0 to 100Hz. Time is indicated on the x-axis and spans 0 to 1000ms. EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

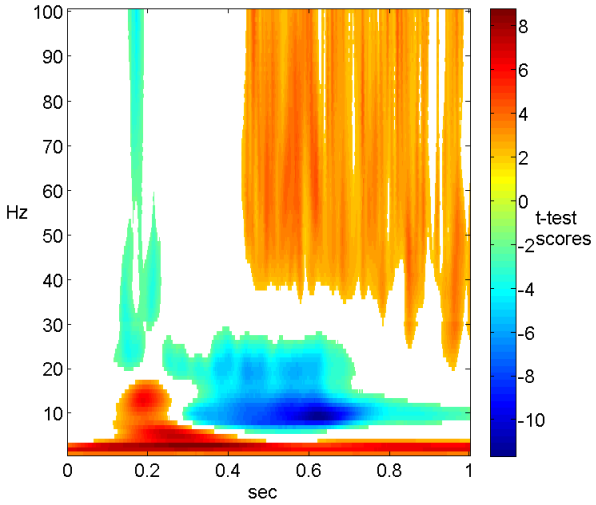
3.3 Oddball task EROs condition effects

Oddball task EROs condition effects in the overall sample (controls, patients, first-degree relatives and ARMS groups combined) are shown in Figure 3.3a. In the studied time-frequency spectrum, target tones elicited larger EROs than non-target tones (positive t-test scores) in the delta/theta frequency range, with maximum difference between approx. 200-400ms post stimulus and in the gamma range, from approx. 500 ms post stimulus; target tones elicited smaller EROs (negative t-test scores) than non-target tones in the alpha/beta frequency range, from approx. 350ms poststimulus and in the gamma range around 200ms poststimulus. When examined separately (Figures 3.3b and 3.3c), the oddball task EROs condition effect shows a similar cluster pattern between patients and controls, except for the late gamma positive cluster, where patients lacked discrimination between target and non-target tones.

Oddball task EROs condition effects

All subjects

a)



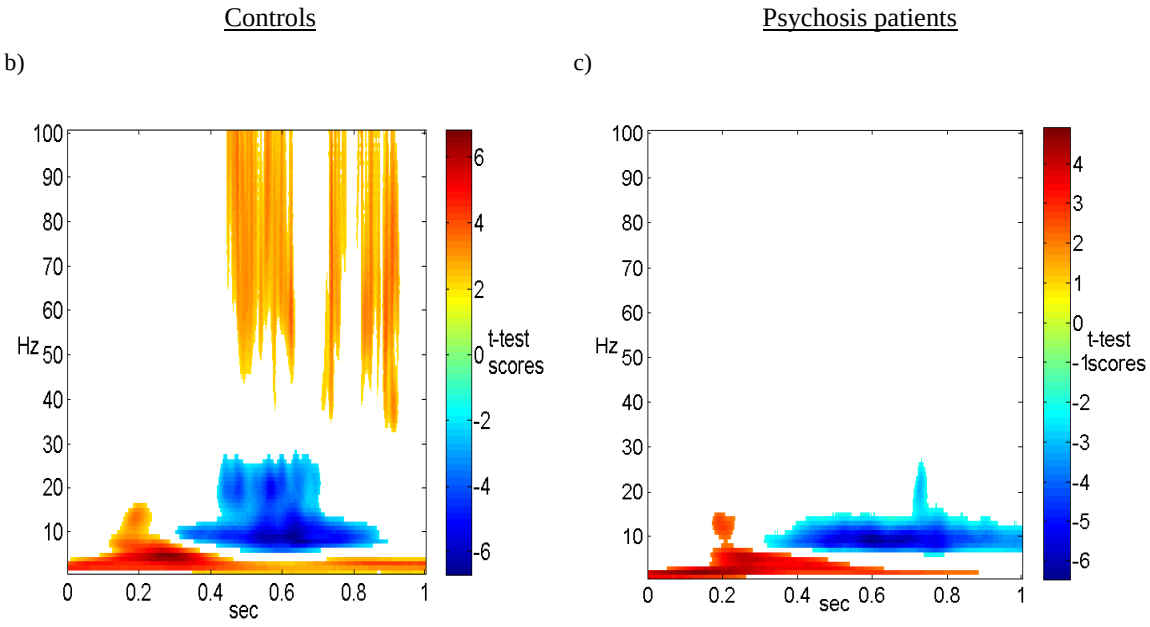


Figure 3.3 T-test comparisons between target Vs non-target tones EROs for a) all subjects combined, b) controls and c) patients groups. EEG frequency is indicated on the y-axis of each plot and spans 0 to 100Hz. Time is indicated on the x-axis and spans 0 to 1000ms. T-test scores are indicated on a colour scale located to the far right of each plot. All results are adjusted for multiple comparisons and a mask (white coulour) applied for non significant comparisons, using a significance threshold of p<.05.

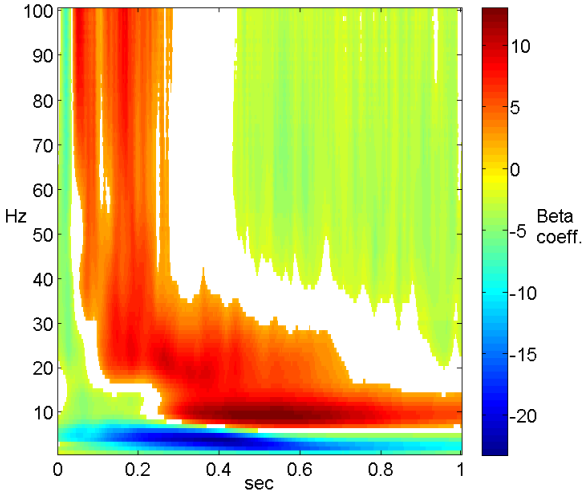
3.4 Oddball task EROs relationships with reaction time

The association between oddball task target tone EROs and reaction time in the overall sample (controls, patients, fisrt-degee relatives and ARMS combined) is shown in Figure 3.4a. Three clusters of linear regression coefficients representing significant associations between target tone EROs and reaction time can be observed. The clusters alternate between negative and positive signals: positive coefficients reflect a direct relationship between EROs and reaction time (the larger EROs, the slower reaction time), whereas negative coefficients represent an inverse relationship (the larger EROs, the faster reaction time). The first cluster is negative and composed of early gamma followed by delta/theta EROs, the second cluster is positive and composed by "mid latency" gamma followed by beta/alpha EROs, the third cluster is negative and composed by late gamma/beta EROs. When examined separately and compared (Figures 3.4b and 3.4c), patients differed from controls in lacking the third cluster.

Oddball task target tone EROs and reaction time

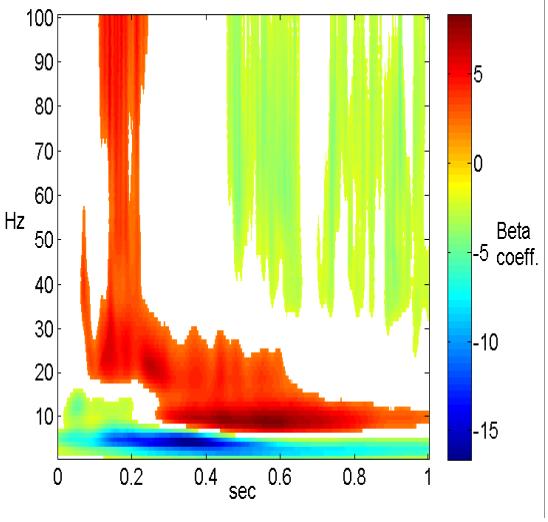
All subjects

a)



Controls

b)



Psychosis patients

c)

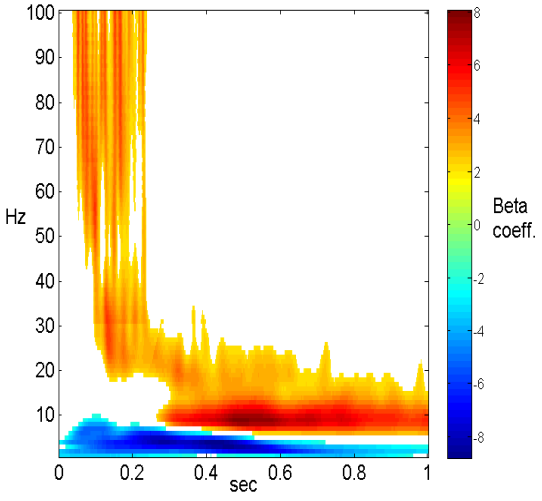


Figure 3.4 Linear regression association between oddball task target tone EROs and reaction time for a) all subjects combined, b) controls and c) patients groups. EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 1000ms; linear regression coefficients results are indicated on a colour scale located to the far right of each plot. Results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. Negative coefficients are represented by "cold" colours whereas positive coefficients are represented by "hot" colours.

3.5 Oddball task EROs relationships with psychosis symptoms

The association between oddball task target tone EROs and PANSS total symptoms score in the patients sample (early psychosis patients and chronic psychosis patients combined) is displayed in Figure 3.5.

The overall pattern of association is similar to that between oddball task target tone EROs and reaction time, with the three regression coefficients clusters described above. There is a negative (inverse) association between the severity of psychosis symptoms as measured by PANSS total score and patients' target tone delta/theta EROs; a positive association with "mid latency" gamma followed by beta/alpha EROs; and again a negative association with late gamma/beta EROs. A similar pattern of associations was observed between the target tone EROs and PANSS positive and negative psychosis symptoms scores, when examined separately (not shown).

Oddball task target tone EROs and PANSS total score

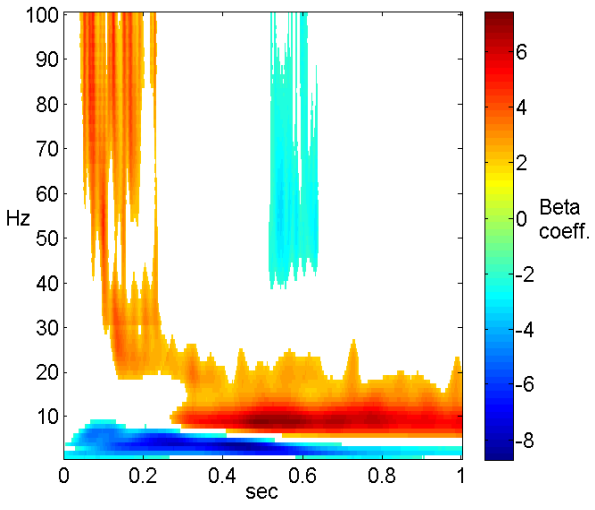


Figure 3.5 Linear regression association between target tone EROs and PANSS total score. EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 1000ms; linear regression coefficients are indicated on a colour scale located to the far right of each plot. Results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. Negative coefficients are represented by "cold" colours whereas positive coefficients are represented by "hot" colours.

3.6 Controls Vs patients' oddball task EROs

The comparison between controls and patients (early psychosis patients and chronic psychosis patients combined) oddball task two tones EROs are displayed in Figure 3.6. T-test scores show reduced delta/theta EROs in patients compared to controls, both for target and for non-target tones, with the largest t-test scores between approx. 200-400ms post stimulus.

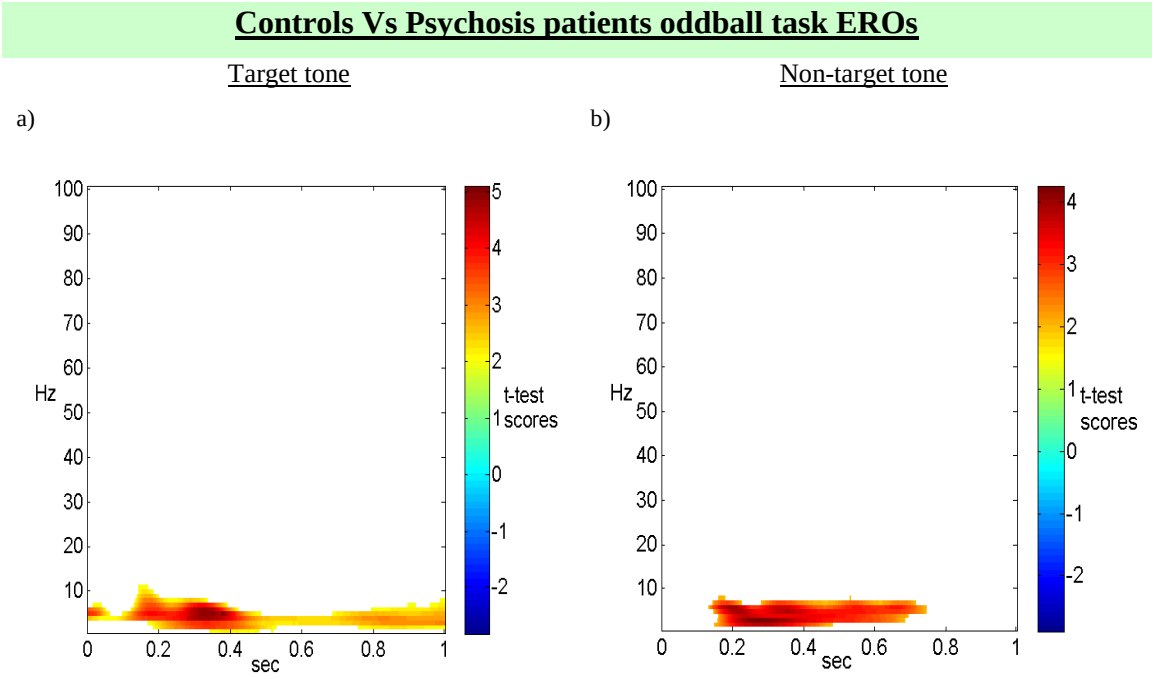


Figure 3.6 T-test scores (colour scale located to the far right of the plot) for comparisons between controls Vs patients a) oddball task target tone EROs and b) oddball task non-target tone EROs. EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 1000ms; t-test scores are indicated on a colour scale located to the far right of each plot. Results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. "Hot" colours represent larger EROs in controls.

3.7 Between-group comparisons of oddball task composite EROs

Relevant oddball task EROs were extracted from the oddball task target tone time-frequency spectrum, based on the observation of the above effects, as indicated in figure 3.7a: 1) a ratio was calculated between target tone EROs measured within the negative clusters and the positive cluster boundaries that were defined by target tone EROs regression with reaction time (Figure 3.4a), taking the maximum EROs value from each cluster. This aims to reflect psychosis related abnormal dynamics between EROs clusters that are functionally linked. 2) that ratio was multiplied by the maximum target tone EROs within the boundaries of the delta/theta cluster defined by target tone between-group comparisons (Figure 3.6a). This aims to reflect a psychosis related deficit in the isolated delta/theta EROs cluster.

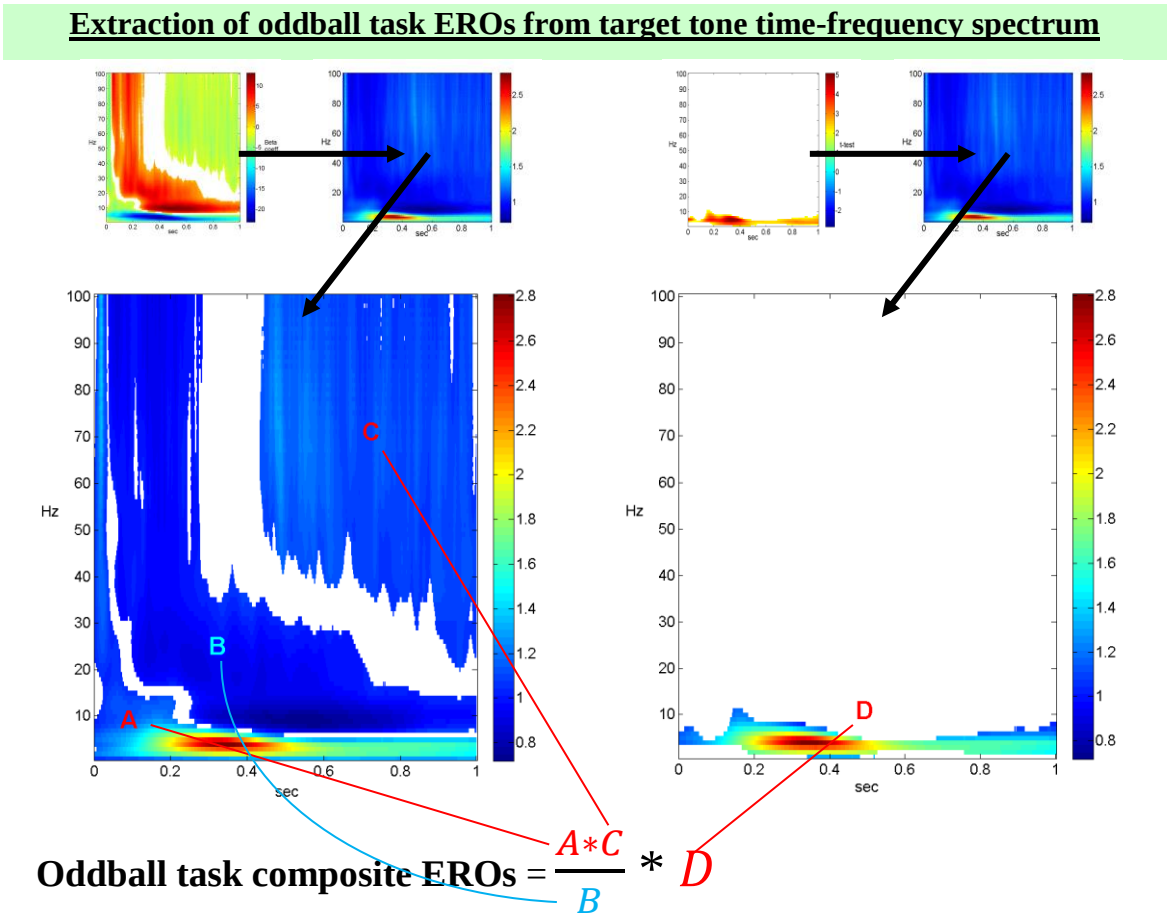


Figure 3.7a The time-frequency boundaries of beta coefficients and t-test clusters scores identified in Figures 3.4a and 3.6a were mapped onto the target tone time-frequency spectrum, extracting four EROs clusters (A, B, C and D), used to calculate oddball task composite EROs. EROs from cluster B are in the fraction denominator because they have an inverse relationship with RT when compared to EROs from cluster A, C and D.

Mean oddball task composite EROs for all the study groups are displayed in Table 3.7a. ANOVA between-group comparisons results are displayed in Table 3.7b. There was a significant main group effect: chronic psychosis patients had smaller oddball task composite EROs than controls, ARMS and first-degree relatives; early psychosis patients had smaller oddball task composite EROs than controls, but not first-degree relatives, nor ARMS subjects; there were no significant differences between controls, ARMS and first-degree relatives groups. There were no significant age, gender, smoking, nor lab main effects.

Oddball task composite EROs

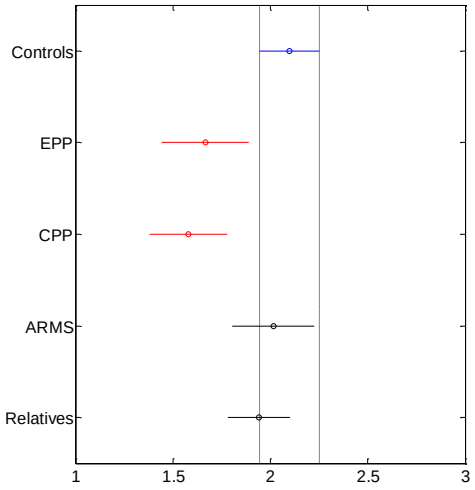


Figure 3.7b: Mean oddball task composite EROs (log transformed) and 95% confidence intervals for the study groups.

Table 3.7a | Odball task composite EROs group means

Controls	EPP	
9.79 (0.70)	6.54 (1.04)	
CPP	**ARMS**	**Relatives**
6.28 (0.93)	8.63 (0.99)	8.78 (0.74)

Table 3.7b | Oddball task composite EROs between-group comparisons

Group comparisons	Est. Mean Difference	95% CI	*F* (p value)
1. Controls Vs EPP	0.43	0.06 to 0.81	5.45 (4,260) p=0.0003
2. Controls Vs CPP	0.52	0.17 to 0.87	
3. Controls Vs ARMS	0.08	-0.28 to 0.45	
4. Controls Vs Relatives	0.16	-0.15 to 0.46	
5. EPP Vs CPP	0.09	-0.33 to 0.51	
6. EPP Vs ARMS	-0.35	-0.78 to 0.08	
7. EPP Vs Relatives	-0.28	-0.66 to 0.11	
8. CPP Vs ARMS	-0.44	-0.85 to -0.03	
9. CPP Vs Relatives	-0.36	-0.72 to -0.004	
10. ARMS Vs Relatives	-0.07	-0.30 to 0.44	

Oddball task composite EROs (log transformed) mean differences between the study groups and 95% confidence intervals, adjusted for multiple comparions. EROs values were log transformed to reduce the skewness of data before ANOVA comparisons. EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

3.8 Oddball task composite EROs and psychosis symptoms

There were no significant associations between PANSS scores in psychosis patients and oddball task composite EROs.

3.9 Oddball task composite EROs deficits - genetic Vs chronicity effects

Results in this chapter show that oddball task composite EROs, which reflect selective attention resource allocation to target tone stimuli processing, were reduced in chronic and early psychosis patients, compared to controls. These EROs were significantly smaller in chronic psychosis patients, but not in early psychosis patients, when compared to the ARMS and first-degree relatives groups. Moreover, ARMs and first-degree relatives groups were not statistically significantly different from either early psychosis patients or controls and had intermediate mean values between the latter groups. This, on the whole, suggests that oddball task composite EROs are impaired by psychosis disease progression and also influenced by genetic liability. This is further discussed in Chapter 7.

CHAPTER FOUR

PASSIVE ODDBALL PARADIGM EROS IN PSYCHOSIS

4.0 Introduction

In this chapter, results are presented in the same structure as of chapter three. Abnormalities in passive oddball paradigm event-related oscillations (EROs) are evaluated as to their influence by genetic liability (as potential endophenotypes for psychosis) and psychosis chronicity. The differences between deviant tone and standard tone EROS responses, that is, condition effects, are examined in order to reveal EROs markers of stimulus salience. The functional role of passive oddball paradigm EROs is further examined by looking at their association with oddball task reaction time (RT), linking passive oddball paradigm EROs to a behavioural response, which is indicative of brain processing speed and attention-related. Passive oddball paradigm EROs possible role in the physiopathology of psychosis symptoms is studied by testing the associations between EROs and PANSS symptoms scores. The effect of psychosis disease on passive oddball paradigm EROs is assessed by comparing controls Vs psychosis patients' deviant and standard tone EROs. After examining those effects, relevant EROs are extracted and compared between all the study groups. The hypothesis here are that: psychosis genetic liability will manifest as reduced EROs in first-degree relatives, compared to healthy subjects and illness chronicity will produce a gradient in passive oddball paradigm EROs: ARMS>early psychosis patients>chronic psychosis

patients. MMN ERP results, although not the main focus of attention in this study, are presented here.

4.1 Between-group comparisons of MMN

Mean MMN amplitude by clinical group and the results of ANOVA between-group comparisons are shown in table 4.1: there was a significant group main effect, where early psychosis patients showed significantly smaller MMN amplitude than all other groups; there were no statistically significant differences between controls, first-degree relatives, ARMS or chronic psychosis patients groups. MMN decreased with age in the overall sample, $F(1,246)=8.33$, $p=0.004$, $\beta=1.72$. Women had larger MMN than men, $F(1,246)=7.56$, $\Delta=-1.05\mu V$, 95% CI= -1.79 to -0.30µV, $p=0.006$. Smoking and testing lab had no main effects on MMN.

MMN

MMN waveforms (Fz)

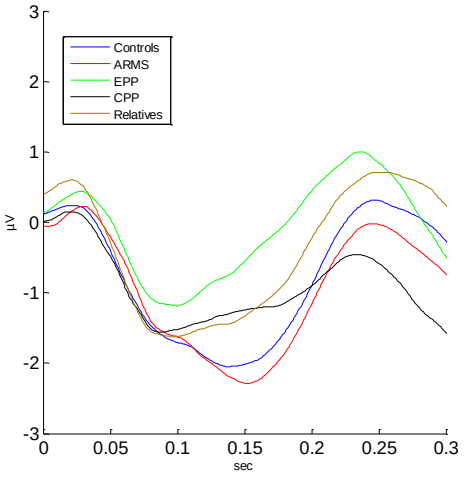


Figure 4.1a MMN grand average waveforms for all study groups. Amplitude (microV) is plotted over time (seconds). Time zero denotes the occurrence of stimuli. Waveforms have been smoothed and the peak of the grand average waveforms does not coincide with the mean of the individual MMN peak amplitudes presented in table 4.1a.

Table 4.1a | MMN amplitude means

Controls	EPP	
-3.46 (0.33)	-1.60 (0.57)	
CPP	**ARMS**	**Relatives**
-3.96 (0.44)	-4.24 (0.59)	-4.11 (0.40)

Mean (standard error) MMN amplitude in µV at Fz electrode, for each study group, adjusted for age and gender.

Table 4.1b | MMN amplitude between-group comparisons

Group comparisons	Est. Mean Difference	95% CI	*F* (df) p value
1. Controls Vs EPP	-1.86	-3.55 to -0.17	**3.57 (4,246) p=0.008**
2. Controls Vs CPP	0.50	-1.03 to 2.03	
3. Controls Vs ARMS	0.78	-1.07 to 2.62	
4. Controls Vs Relatives	0.65	-0.85 to 2.14	
5. EPP Vs CPP	2.36	0.36 to 4.36	
6. EPP Vs ARMS	2.63	0.40 to 4.87	
7. EPP Vs Relatives	2.51	0.38 to 4.63	
8. CPP Vs ARMS	0.27	-1.80 to 2.36	
9. CPP Vs Relatives	0.15	-1.42 to 1.71	
10. ARMS Vs Relatives	-0.13	-2.19 to 1.93	

MMN amplitude estimated mean differences between the study groups and 95% confidence intervals, adjusted for multiple comparisons. EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

4.2 Passive oddball paradigm EROs time-frequency plots

Passive oddball paradigm EROs time-frequency plots for both deviant and standard tone, by study group, are displayed in Figure 4.2.

Passive oddball EROs time-frequency plots

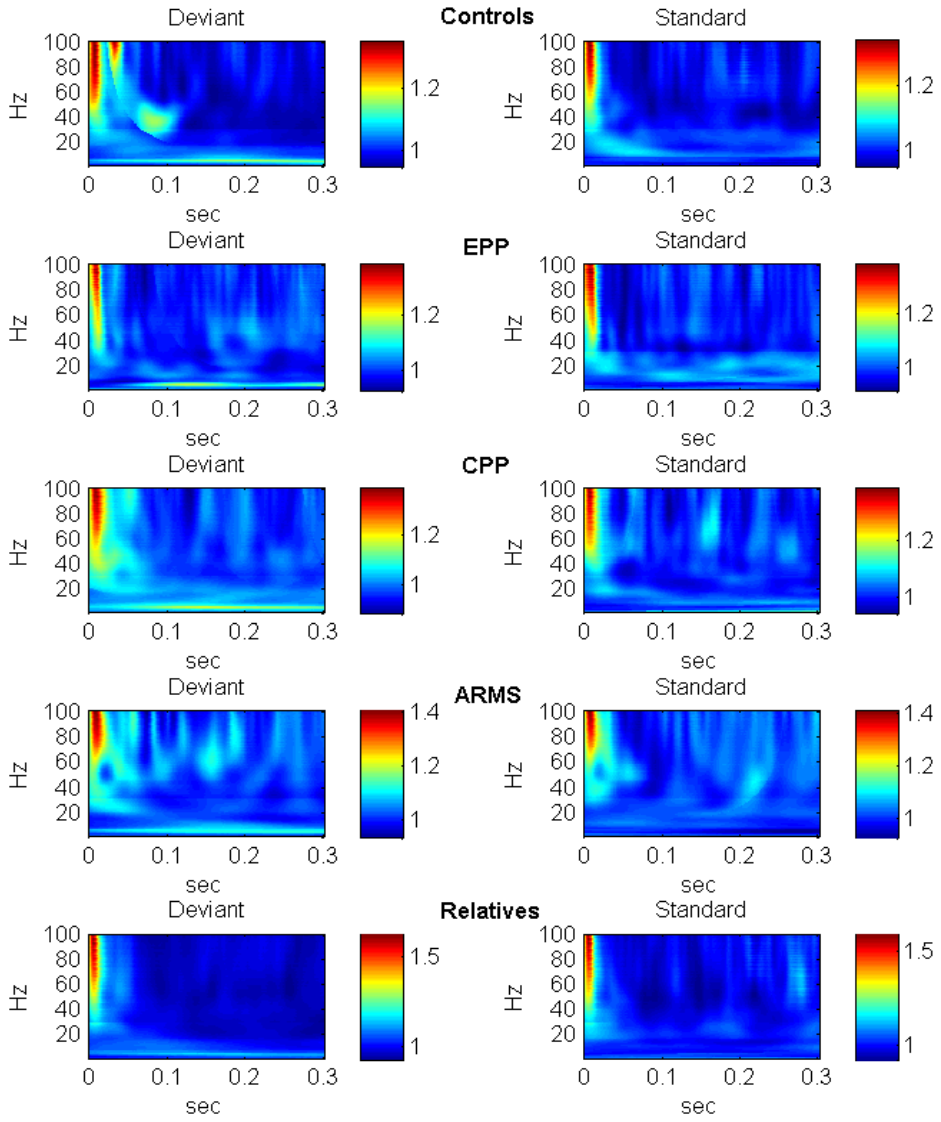


Figure 4.2 The EROs time-frequency plots depict mean change in power, in relation to the prestimulus baseline, for passive oddball paradigm deviant (left) and standard (right) tones and for each study group (different rows). EEG frequency is indicated on the y-axis of each plot and spans 0 to 100Hz. Time is indicated on the x-axis and spans 0 to 300ms. EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

4.3 Passive oddball paradigm EROs condition effects

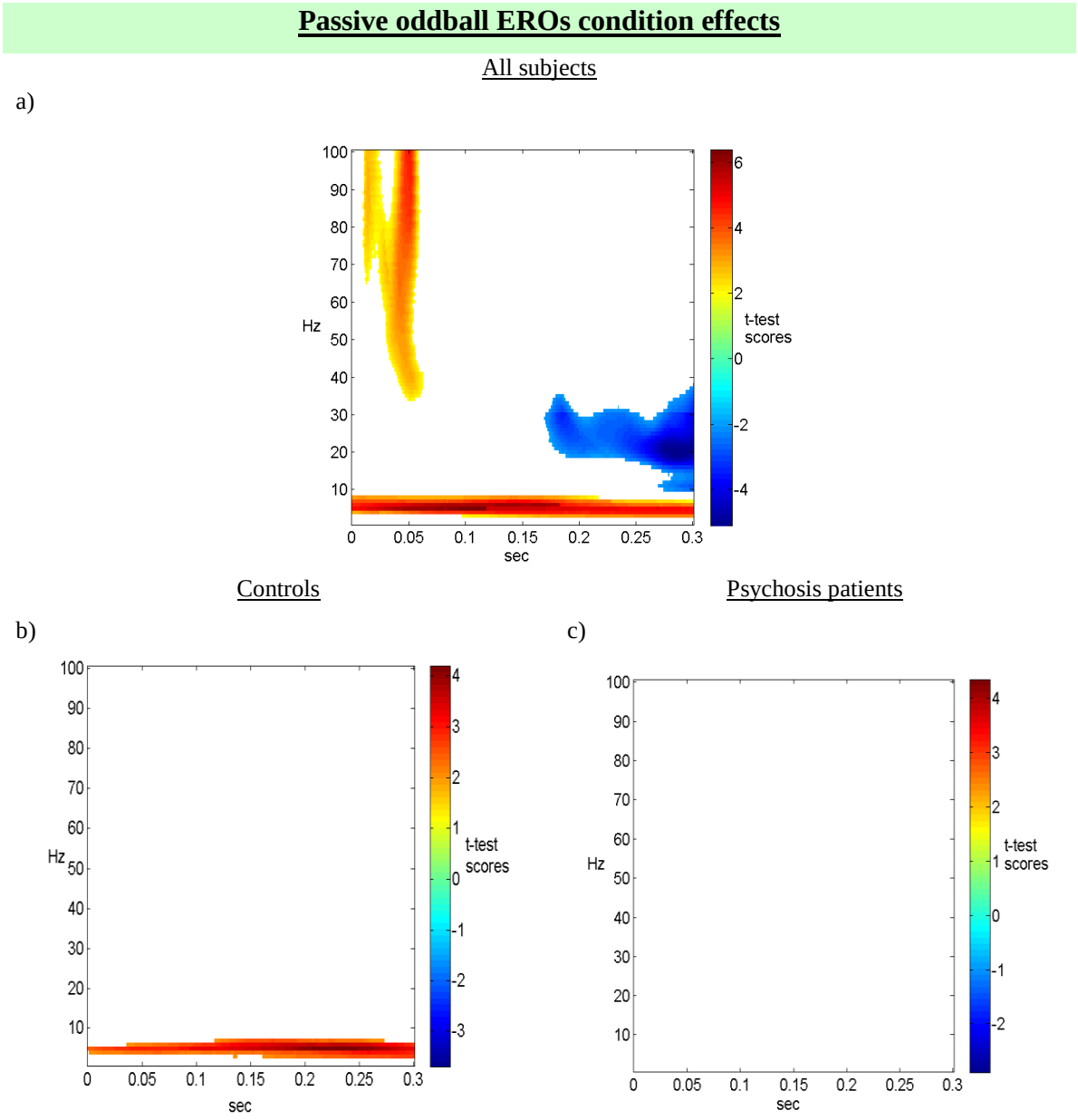


Figure 4.3 T-test scores for comparisons between passive oddball paradigm deviant Vs standard tone EROs for a) all subjects combined, b) controls and c) psychosis patients. EEG frequency is indicated on the y-axis of each plot and spans 0 to 100Hz. Time is indicated on the x-axis and spans 0 to 300ms. T-test scores are indicated on a colour scale located to the far right of each plot. All results are adjusted for multiple comparisons and a mask (white coulour) applied for non significant comparisons, using a significance threshold of p<.05.

Passive oddball paradigm EROs condition (deviant Vs standard tones) effects in the overall study sample (controls, patients, first-degree relatives and ARMS combined) are shown in figure 4.3. Deviant tones elicited larger early (up to approx. 40ms post

stimulus) gamma EROs and larger delta/theta EROs than standard tones throughout the studied time interval, with maximum t-test values approx. between 50-150ms; deviant tones elicited less beta EROs than standard tones (from approx. 175ms post stimulus). When examining EROs condition effects separately in controls and patients groups, only the delta/theta EROs cluster is present in controls and no difference between the two tone types is observed in psychosis patients.

4.4 Passive oddball paradigm EROs relationships with oddball task reaction time

The associations between deviant tone EROs / the difference deviant-standard tone EROs and oddball task reaction time (RT) in the overall study sample (controls, patients, first-degree relatives and ARMS combined) are shown in Figure 4.4a and 4.4b respectively. In Figure 4.4a, two clusters of linear regression coefficients representing significant associations between deviant tone EROs and RT can be observed. The 1st cluster and 2nd cluster have respectively negative and positive coefficients: negative coefficients reflect an inverse relationship (the larger EROs, the faster RT), whereas positive coefficients represent a direct relationship between EROs and RT (the larger EROs, the slower RT). The first cluster is composed of early gamma EROs and delta/theta EROs, the second is composed by gamma/beta EROs. When the patterns of associations between deviant tone EROs and RT were examined separately for patients and controls (not shown), they did not differ from the above. In Figure 4.4b, significant clusters overlap with the previously described clusters in Figure 4.4a, but more circumscribed in the time-frequency spectrum.

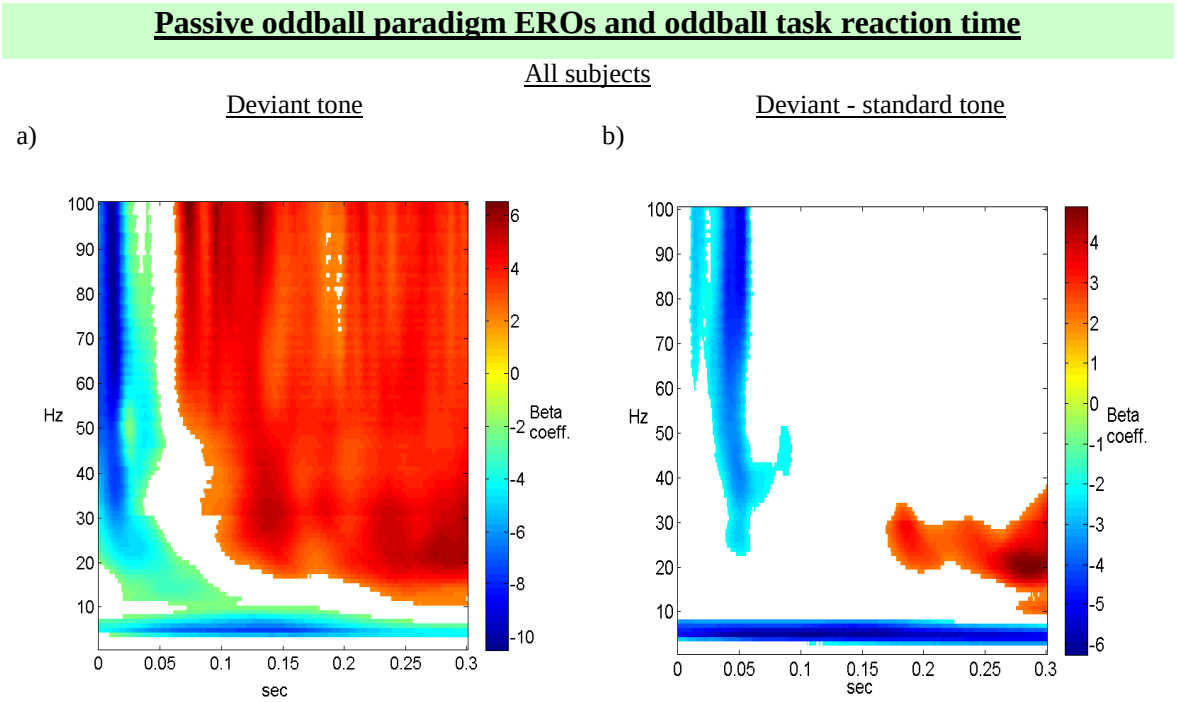


Figure 4.4 Linear regression association between a) deviant tone EROs and oddball task reaction time (RT), b) deviant-standard tone EROs and RT. EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 300ms; linear regression coefficients are indicated on a colour scale located to the far right of each plot. Results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. Negative coefficients are represented by "cold" colours whereas positive coefficients are represented by "hot" colours.

4.5 Passive oddball EROs relationships with psychosis symptoms

The associations between deviant tone EROs / the difference deviant-standard tone EROs and PANSS total symptoms score in the patients sample (early psychosis patients and chronic psychosis patients combined) is displayed in figure 4.5.

The pattern of associations partially overlaps with that between passive oddball EROs and oddball task reaction time described in 4.5. There is a negative (inverse) association between the severity of psychosis symptoms as measured by PANSS total scores and patients' deviant tone early gamma EROs; a positive association with deviant tone late gamma/beta EROs; a positive association with deviant-standard tone late beta EROs. A similar pattern of clusters was observed when PANSS positive and negative symptoms scores were used in place of PANSS total scores (not shown).

Passive oddball paradigm EROs and PANSS total score

a) Deviant tone

b) Deviant - standard tone

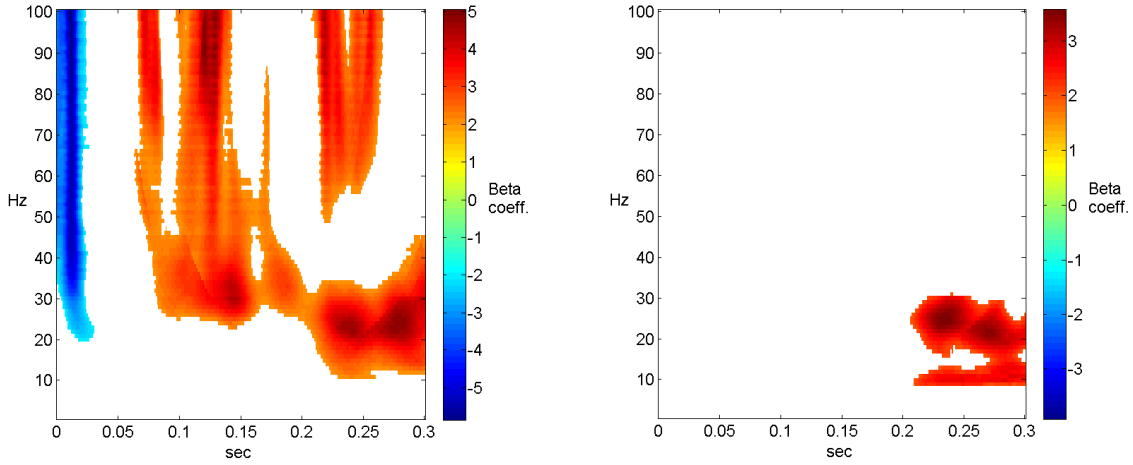


Figure 4.5 Linear regression association between a) deviant tone EROs and PANSS total score, b) deviant-standard tones EROs difference and PANSS total score. EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 300ms; linear regression coefficients are indicated on a colour scale located to the far right of each plot. Results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. Negative coefficients are represented by "cold" colours whereas positive coefficients are represented by "hot" colours.

4.6 Controls Vs patients' passive oddball paradigm EROs

There were no significant differences between controls' and patients' deviant tone, standard tone or deviant-standard tone EROs.

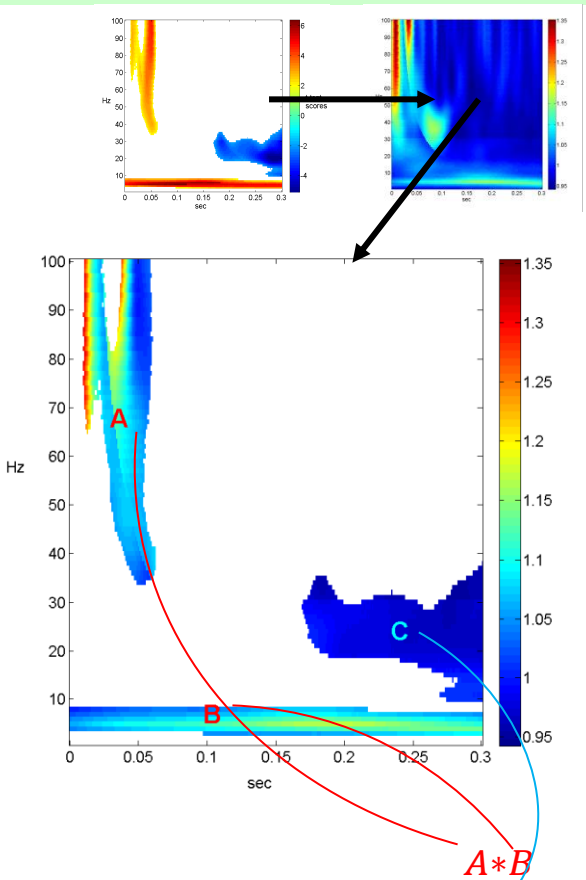
4.7 Between-group comparisons of passive oddball paradigm composite EROs

Relevant passive oddball paradigm composite EROs were extracted based on the observation of the above effects, indicated in Figure 4.7a.

The ratio was calculated between EROs within the gamma and theta positive clusters boundaries and EROs within the beta negative cluster boundaries, defined by the passive oddball paradigm EROs condition effects (Figure 4.7a), taking the maximum

EROs value from each cluster. This aims to reflect psychosis related abnormal dynamics between EROs clusters that are functionally linked. Unlike in oddball task EROs extraction, this ratio was not weighed to reflect deviant tone EROs patients Vs controls groups differences, given these were statistically non significant.

Extraction of passive oddball paradigm EROs from deviant tone time-frequency spectrum



Passive oddball paradigm composite EROs = $\frac{A*B}{C}$

Figure 4.7a The time-frequency boundaries of t-test clusters scores identified in Figure 4.3a were mapped onto the deviant tone time-frequency spectrum, extracting three EROs clusters (A, B and C), used in the fraction above to calculate passive oddball paradigm composite EROs. EROs from cluster C are in the fraction denominator because they show an inverse condition effect compared to EROs from clusters A and B.

Mean passive oddball paradigm composite EROs for all the study groups are displayed Table 4.7a. ANOVA between-group comparisons results are displayed in Table 4.7b and show a significant main effect for group: there was a trend for larger passive

oddball paradigm composite EROs in controls, compared to early psychosis patients; first-degree relatives showed a larger ratio than controls, early psychosis patients and ARMS subjects, but no significant difference to chronic psychosis patients; early psychosis patients showed a smaller ratio than chronic psychosis patients but no significant difference to ARMS subjects. There was a significant age effect, $F(1,246)=9.35$, $p=0.002$, where passive oddball paradigm composite EROs decreased with age ($\beta=-0.16$). Gender, smoking and lab had no statistically significant effect on passive oddball paradigm composite EROs.

Passive oddball paradigm composite EROs

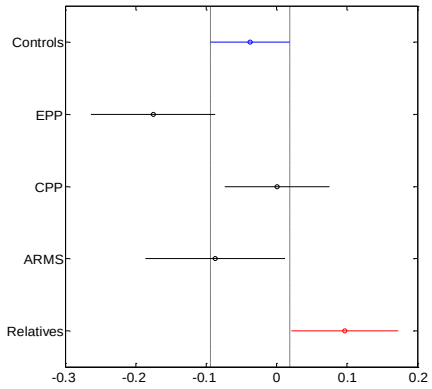


Figure 4.7b: Mean passive oddball paradigm composite EROs (log transformed) and 95% confidence intervals for the study groups, adjusted for age.

Table 4.7a | Passive oddball paradigm composite EROs group means

Controls	EPP		
0.99 (0.03)	0.85 (0.05)		
CPP	**ARMS**	**Relatives**	
1.04 (0.04)	0.93 (0.06)	1.15 (0.04)	

Mean (se) passive oddball paradigm composite EROs for the study groups, adjusted for age.

Table 4.7b | Passive oddball paradigm composite EROs between-group comparisons

Group comparisons	Est. Mean Difference	95% CI	*F* (df) p value
1. Controls Vs EPP	0.14	-0.006 to 0.28	4.7 (4,246) p=0.001
2. Controls Vs CPP	-0.04	-0.17 to 0.09	
3. Controls Vs ARMS	0.05	-0.11 to 0.20	
4. Controls Vs Relatives	-0.13	-0.26 to -0.004	
5. EPP Vs CPP	-0.18	-0.34 to -0.008	
6. EPP Vs ARMS	-0.09	-0.26 to 0.08	
7. EPP Vs Relatives	-0.27	-0.44 to -0.10	
8. CPP Vs ARMS	-0.09	-0.09 to 0.27	
9. CPP Vs Relatives	-0.10	-0.23 to 0.04	
10. ARMS Vs Relatives	-0.18	-0.18 to -0.00005	

Passive oddball paradigm composite EROs (log transformed) mean differences between the study groups and 95% confidence intervals. adjusted for multiple comparions. EROs values were log transformed to reduce the skewness of data before ANOVA comparisons. EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

4.8 Passive oddball paradigm composite EROs and psychosis symptoms

There was a significant association between passive oddball paradigm composite EROs and PANSS negative symptoms scores in chronic psychosis patients (Figure 4.8, R^2 linear=0.21, r= 0.46, p<0.01), but not in early psychosis patients. In chronic patients, the larger passive oddball paradigm composite EROs, the less severe psychosis negative symptoms.

Passive oddball paradigm composite EROs and psychosis symptoms in chronic psychosis

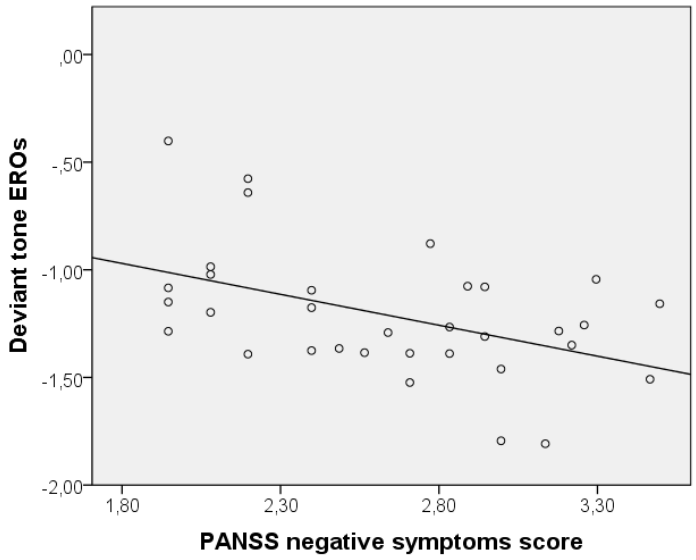


Figure 4.8 Scatter plot and fitted regression line showing the relationship between passive oddball paradigm composite EROs and PANSS negative symptoms scores, in the chronic psychosis patients sample. EROs and PANSS scores have been log transformed.

4.9 Passive oddball paradigm composite EROs abnormalities - genetic Vs chronicity effects

Larger passive oddball paradigm composite EROs correspond to larger deviant tone EROs modulation in the time-frequency regions of interest, indicating stronger stimulus salience attribution and resulting in faster RT. Results in the chapter show that, after adjustment for age, passive oddball paradigm composite EROs were overly large in first-degree relatives, compared to controls, indicating a psychosis associated genetic influence on those EROs. The fact that genetically liable but disease-free and assymptomatic subjects had increased passive oddball paradigm composite EROs compared to controls, suggests this may be a compensatory mechanism. Chronic psychosis patients show larger passive oddball paradigm composite EROs than early psychosis patients, which means that psychosis patients are able, over time and as they get distanced from disease onset, to enhance this brain function. Moreover, in the chronic patients group, having larger passive oddball paradigm composite EROs was linked to showing less psychosis symptoms. Passive oddball paradigm composite EROs are therefore influenced by both psychosis genetic liability and disease progression. This is further discussed in Chapter 7.

CHAPTER FIVE

PAIRED-CLICK PARADIGM EROS IN PSYCHOSIS

5.0 Introduction

In this chapter, results are presented in a similar structure as in chapters three and four. Abnormalities in paired-click paradigm EROs are evaluated as to their influence by genetic liability and psychosis disease chronicity. The dynamics of paired-click paradigm EROs in evaluated by examining condition effects, that is, the differences between S1 (conditioning) tone and S2 (test) tone EROs, which should reveal neurophysiological markers of brain sensory gating mechanisms. The functional role of paired-click paradigm EROs is further examined by looking at their association with oddball task reaction time, linking sensory gating brain mechanisms with a behavioural response that is indicative of brain processing speed and attention-related. The relationships between paired-click paradigm EROs and psychosis symptoms are studied by testing their associations with PANSS scores. The effect of psychosis disease on paired-click paradigm EROs is assessed by comparing controls Vs psychosis patients S1, S2 and S2/S1 EROs. After examining the above effects, relevant EROs are extracted and compared between all the study groups. The hypothesis here are that: psychosis genetic liability will manifest as reduced paired-click paradigm EROs in first-degree relatives, compared to healthy subjects and that illness chronicity will produce a gradient in paired-click paradigm EROs: ARMS<early psychosis patients<chronic psychosis patients. P50 ERP ratio results, although not the main focus of attention in this study, are presented here.

5.1 Between-group comparisons of P50 ratio

Mean P50 ratio by clinical group and the results of the ANOVA group comparisons are shown in table 5.1: there was a significant group main effect, where chronic psychosis patients had larger P50 ratio than controls and first-degree relatives groups; and there were no statistically significant differences between the controls, early psychosis patients, first-degree relatives, or ARMS groups. P50 ratio increased (meaning worsening gating) with age in the overall sample, $F(1,218)=6.69$, $p=0.01$, $\beta=0.007$. No significant main effects for gender, smoking or lab were found.

P50 ratio

P50/N100 waveforms (Cz)

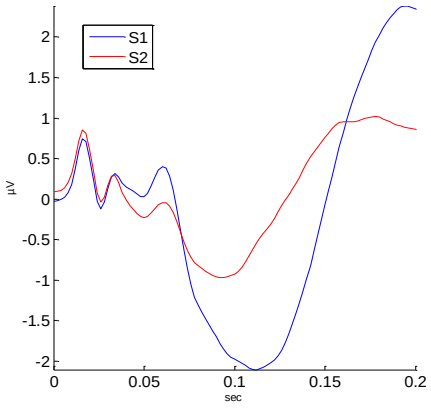


Figure 5.1 P50 grand average ERP waveforms for the overall study sample. Amplitude (microV) is plotted over time (seconds). Waveforms have been smoothed with a 10ms time window.

Table 5.1a | P50 ratio means

Controls	EPP	
0.51 (0.06)	0.72 (0.10)	
CPP	**ARMS**	**Relatives**
0.90 (0.08)	0.65 (0.11)	0.46 (0.07)

Mean (standard error) P50 ratios (S2 P50 amplitude/S1 P50 amplitude) at Cz electrode, for the study groups. The P50 ratio is adjusted for age.

Table 5.1b | P50 ratio between-group comparisons

Group comparisons	Est. Mean Difference	95% CI	*F* (df) p value
1. Controls Vs EPP	-0,20	-0,52 to 0.12	5.25 (4,218) p=0.0005
2. Controls Vs CPP	-0,39	-0,68 to -0.10	
3. Controls Vs ARMS	-0,14	-0,47 to 0.19	
4. Controls Vs Relatives	0,05	-0,22 to 0.32	
5. EPP Vs CPP	-0,19	-0,55 to 0.17	
6. EPP Vs ARMS	0,06	-0,31 to 0.44	
7. EPP Vs Relatives	0,26	-0,11 to 0.62	
8. CPP Vs ARMS	0,25	-0,12 to 0.62	
9. CPP Vs Relatives	0,44	0,15 to 0.74	
10. ARMS Vs Relatives	0,19	-0,18 to 0.56	

P50 ratio estimated mean differences between the study groups and 95% confidence intervals, adjusted for multiple comparisons. EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

5.2 Paired-click paradigm EROs time-frequency plots

Paired-click paradigm S2/S1 tone EROs time-frequency plots, by study group, are displayed in Figure 5.2.

Paired-click paradigm S2/S1 tone ERO time-frequency plots

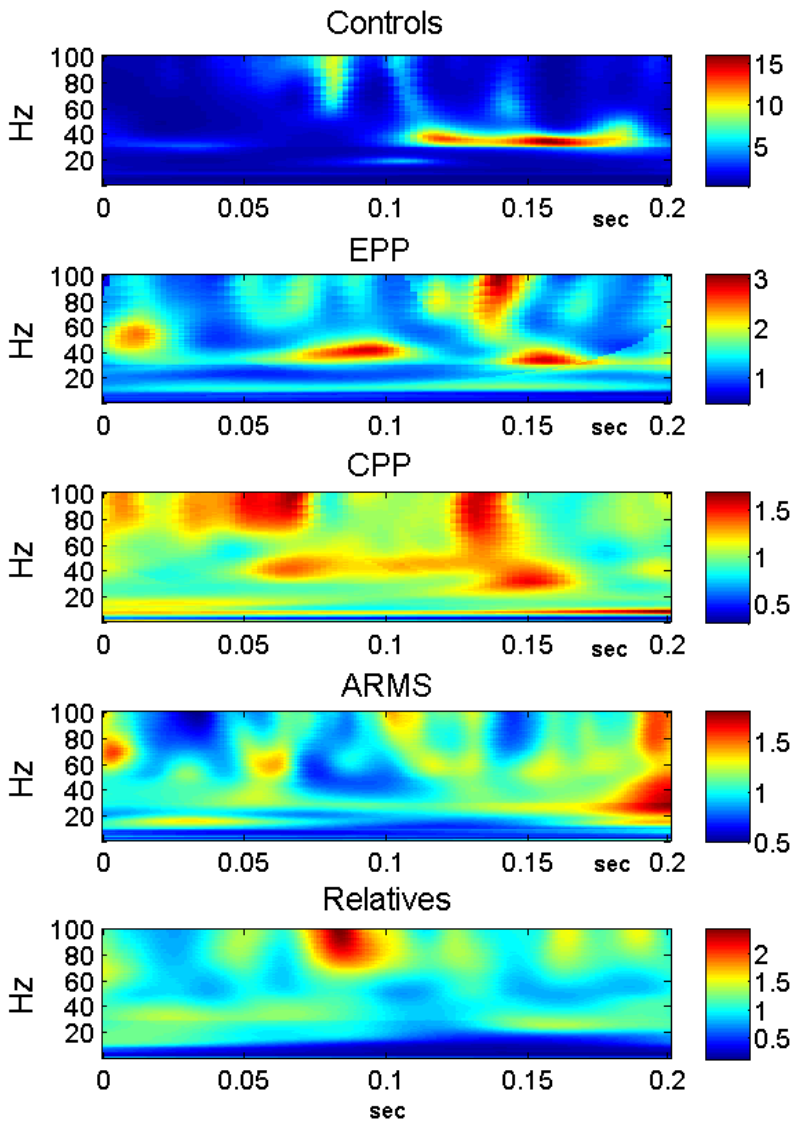


Figure 5.2 The time-frequency plots depict S2/S1 tone EROs, for each study group (different rows). EEG frequency is indicated on the y-axis of each plot and spans 0 to 100Hz. Time is indicated on the x-axis and spans 0 to 300ms. EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

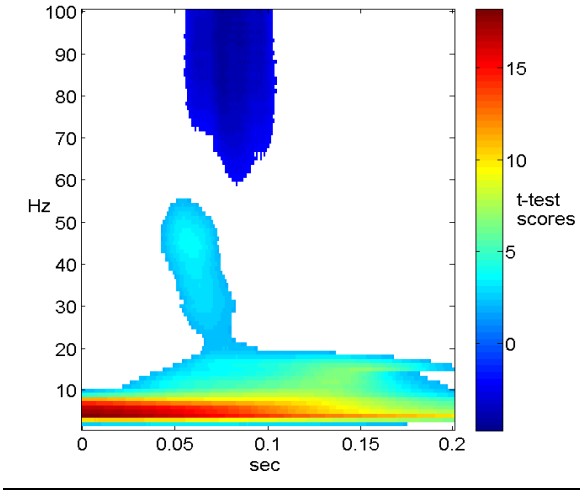
5.3 Paired-click paradigm EROs condition effects

Paired-click paradigm EROs condition effects in the overall sample (controls, patients, first-degree relatives and ARMS groups combined) are shown in figure 5.3.

Paired-click paradigm EROs condition effects

All subjects

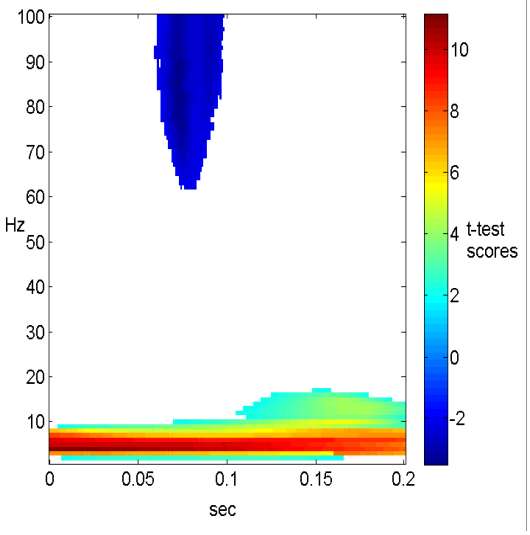
a)



Controls

Psychosis patients

b)



c)

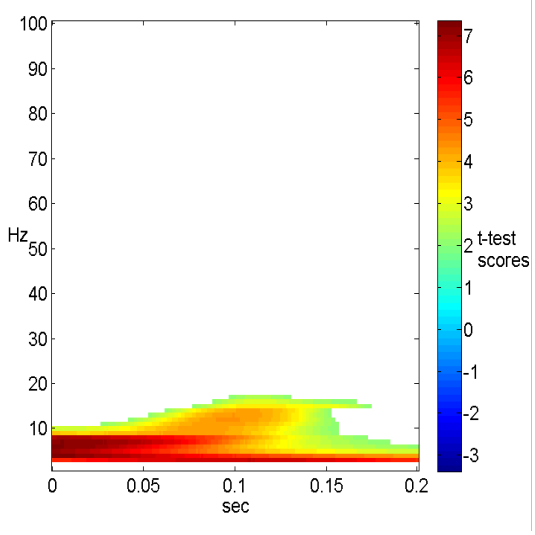


Figure 5.3 t-test scores for comparisons between S1 Vs S2 tones EROs are presented for a) all subjects combined, b) controls and c) patients. EEG frequency is indicated on the y-axis of each plot and spans 0 to 100Hz. Time is indicated on the x-axis and spans 0 to 200ms. T-test scores are indicated on a colour scale located to the far right of each plot. All results are adjusted for multiple comparisons and a mask (white coulour) applied for non significant comparisons, using a significance threshold of $p<.05$.

S1 tones elicit larger delta/theta EROs than S2 tones, with decreasing t-test values along the studied interval time axis. S1 tones elicit smaller gamma EROs than S2 tones between approx. 50-100ms post stimulus. The gamma EROs condition effect is not observed when examining patients responses separately.

5.4 Paired-click paradigm EROs relationships with oddball task reaction time

The association between S1 EROs, S2 EROs, S2/S1 EROs ratio and oddball task reaction time (RT) in the overall sample (controls, patients, first-degree relatives and ARMS groups combined) are shown in figure 5.4.

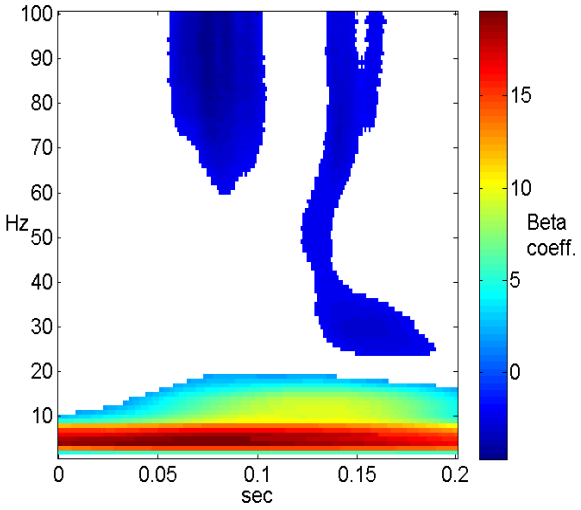
Three clusters of linear regression coefficients representing significant associations between S2/S1 EROs ratio and oddball task RT can be observed. Two clusters have negative signals and one has positive signal: positive coefficients reflect a direct relationship between sensory EROs ratio and RT (the larger the ratio, or the worse sensory EROs gating is, the slower RT); negative coefficients represent an inverse relationship (the opposite relationship between sensory EROs ratio and RT). The two negative clusters are composed first of early gamma, followed by gamma/beta EROs. The gamma EROs cluster is between approx 50-100ms post stimulus, between the P50 and N100 ERP peaks. The positive cluster is composed by delta/theta EROs and spans the studied time interval (0-200ms).

The associations between S1 EROs and RT form similar clusters to the ones described above, except with opposite signals and one can observe the delta/theta cluster "extending" earlier in time to gamma frequencies.

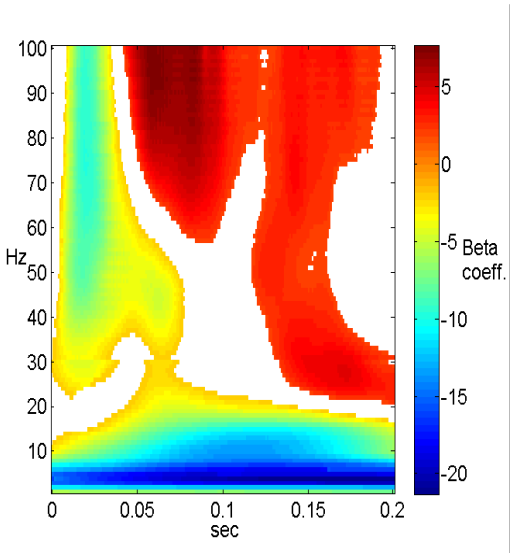
The associations between S2 EROs and RT form two clusters. The positive cluster is composed of delta/theta EROs and the negative cluster is composed of early gamma EROs followed by later beta/alpha EROs.

Paired-click paradigm EROs and oddball task reaction time (RT)

a) S2/S1 EROs ratio and oddball task RT



b) S1 EROs and oddball task RT



c) S2 EROs and oddball task RT

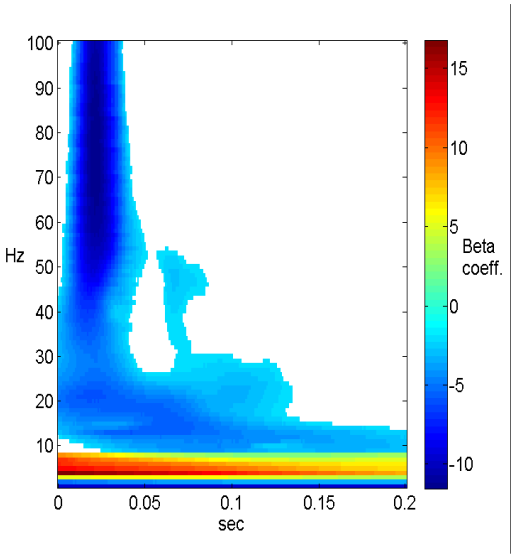


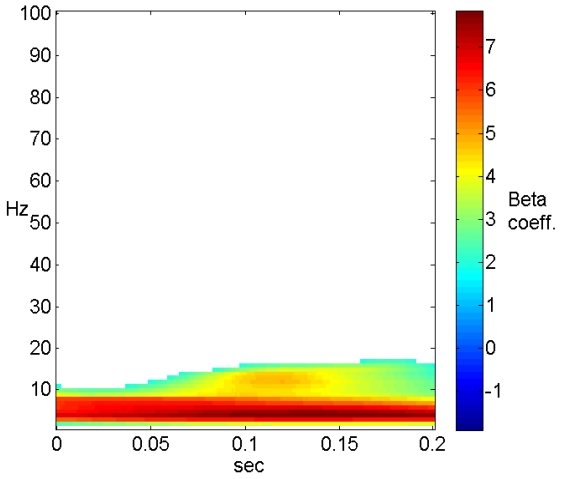
Figure 5.4 Linear regression associations between oddball task reaction time and paired-click paradigm a) S2/S1 EROs ratio, b) S1 and c) S2 EROs. All subjects were included in this analyses (controls, first-degree relatives, patients and ARMS groups combined). EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 200ms; linear regression coefficients are indicated on a colour scale located to the far right of each plot. Results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. Negative coefficients are represented by "cold" colours whereas positive coefficients are represented by "hot" colours.

5.5 Paired-click paradigm EROs relationships with psychosis symptoms

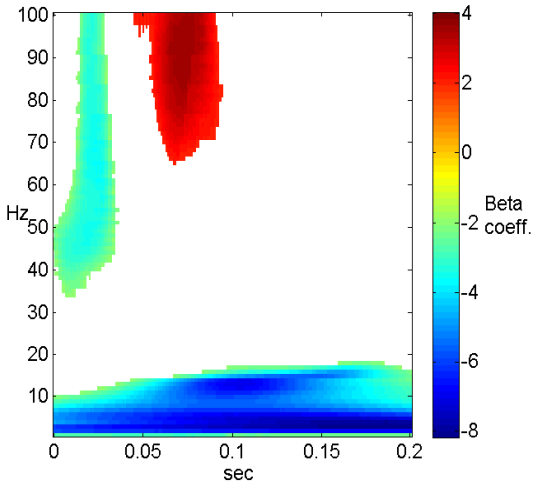
The association between paired-click paradigm EROs and PANSS total symptoms score in the patients sample (early psychosis patients and chronic psychosis patients combined) is displayed in figure 5.5.

Paired-click paradigm EROs and PANSS total score

a) S2/S1 EROs ratio and PANSS total score



b) S1 EROs and PANSS total score



c) S2 EROs and PANSS total score

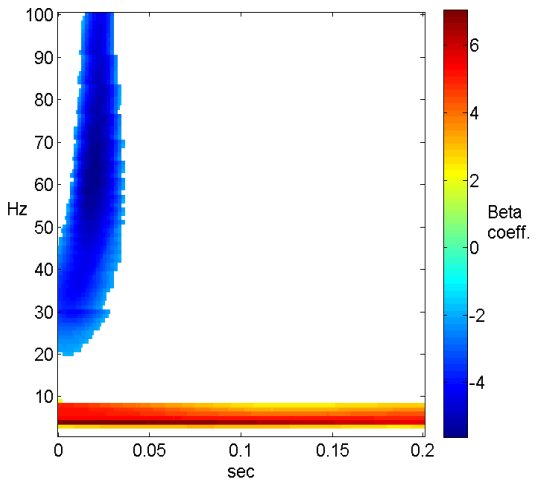


Figure 5.5 Linear regression associations between PANSS total scores and a) S2/S1 EROs ratio, b) S1 and c) S2 EROs. All patients for whom EEG and symptoms data were available were included in this analyses (early psychosis and chronic psychosis patients combined). EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 200ms; linear regression coefficients are indicated on a colour scale located to the far right of each plot. Results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. Negative coefficients are represented by "cold" colours whereas positive coefficients are represented by "hot" colours.

The overall pattern of association is similar to that between S2/S1 EROs ratio and RT, with the regression coefficients clusters described above, but more circunscribed in their time-frequency boundaries. The gamma cluster is absent from the S2/S1 EROs ratio association with psychosis symptoms.

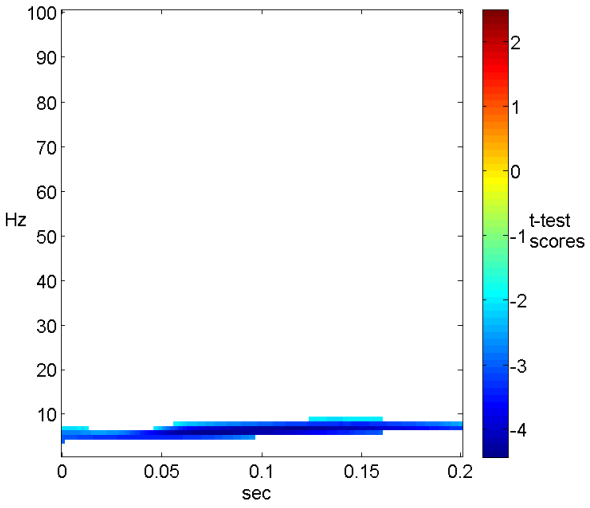
5.6 Controls Vs patients paired-click paradigm EROs

The comparisons between controls and patients (early psychosis patients and chronic psychosis patients combined) paired-click paradigm EROs time-frequency spectrums are displayed in figure 5.6.

T-test scores show increased S2/S1 theta EROs ratio in patients, compared to controls, across the studied time interval. Controls show larger EROs than patients for both S1 and S2 conditions, in an early time window centered on alpha/lower beta range oscillations.

Paired-click paradigm EROs - Controls Vs Patients

a) S2/S1 EROs ratio



b) S1 EROs

c) S2 EROs

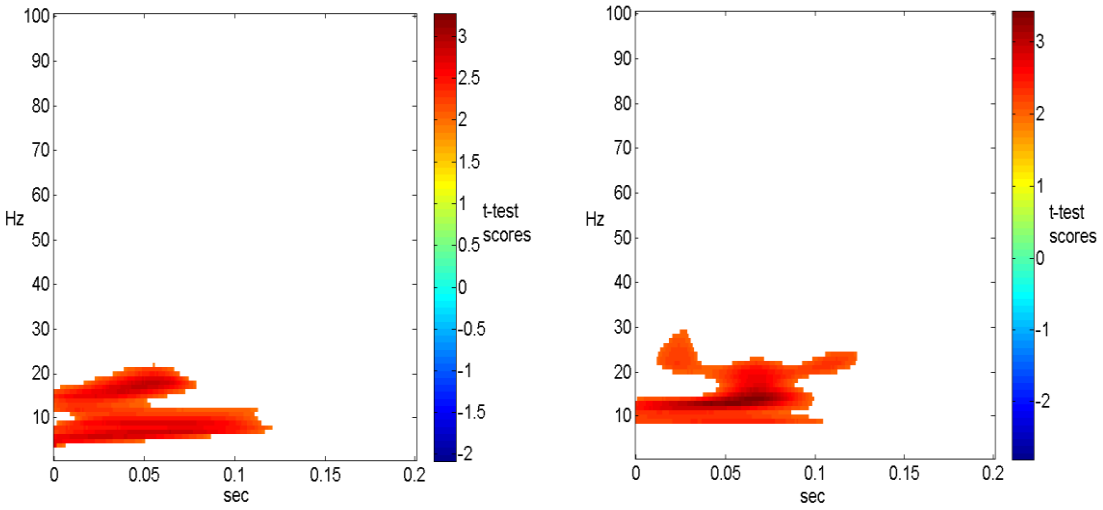


Figure 5.6 T-test scores (colour scale located to the far right of the plot) for comparisons between controls Vs patients a) S2/S1 EROs ratio, b) S1 tone EROs and c) S2 tone EROs. EEG frequency is indicated on the y-axis and spans 0 to 100Hz; time is indicated on the x-axis and spans 0 to 200ms; results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$.

5.7 Between-group comparisons of paired-click paradigm composite EROs

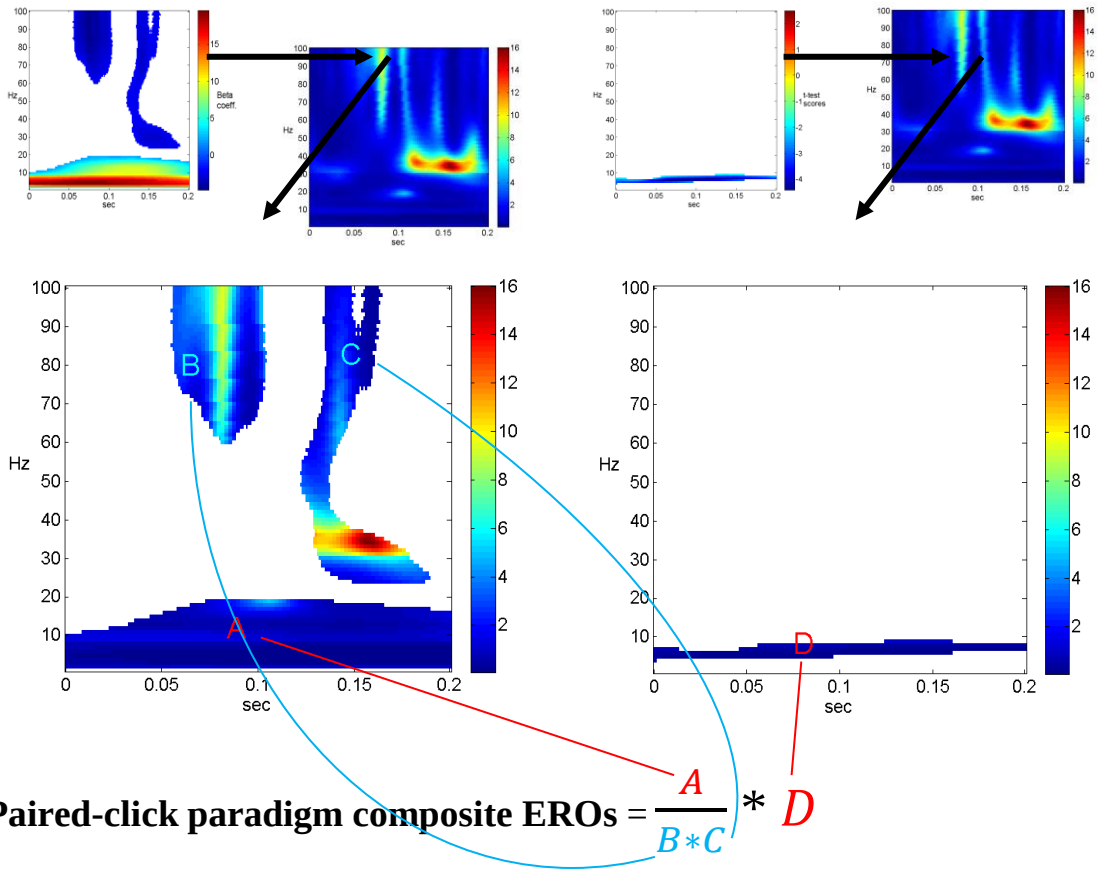
Relevant paired-click paradigm EROS were extracted from S2/S1 tone time-frequency spectrum, based on the observation of the above effects, as indicated in Figure 5.7a:

1) S2/S1 EROs time-frequency spectrum was computed;

2) from S2/S1 EROs, the ratio between values within the time-frequency boundaries of the positive theta cluster and the negative gamma/beta clusters associated with oddball task reaction time (Figure 5.4a) was calculated, taking the maximum EROs value from each cluster. This aims to reflect psychosis related abnormal dynamics between paired-click paradigm EROs clusters that are functionally linked.

3) this ratio was finally multiplied by the minimum S2/S1 EROs value within the boundaries of the negative theta cluster from group comparisons (Figure 5.6a). This aims to reflect a psychosis related gating deficit in the isolated delta/theta cluster.

Figure 5.7a: Extraction of paired-click paradigm EROs from S2/S1 EROs time-frequency spectrum



The time-frequency boundaries of beta coefficients and t-test clusters scores identified in Figures 5.4a and 5.6a were mapped onto S2/S1 EROs time-frequency spectrum, extracting four EROs clusters (A, B, C and D), used to calculate paired-click paradigm composite EROs. EROs from cluster B and C are in the fraction denominator because they have an inverse relationship with RT when compared to EROs from cluster A and D.

Mean paired-click paradigm composite EROs for all the study groups are displayed in Table 5.7a. ANOVA between-group comparisons results are displayed in Table 5.7b and show a significant main effect for group: controls showed smaller paired-click paradigm composite EROs than early and chronic psychosis patients. ARMS subjects

showed smaller values than early psychosis patients, chronic psychosis patients and first-degree relatives. The latter group did not differ from controls nor patients and showed a mean intermediate value between them. Age, gender, smoking and lab had no statistically significant effect on paired-click paradigm composite EROs.

Paired-click paradigm composite EROs

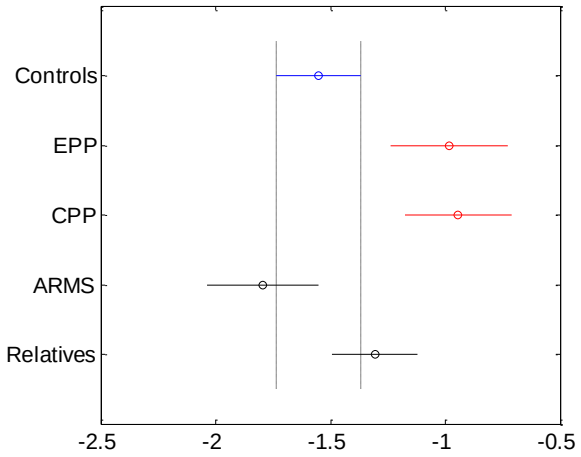


Figure 5.7b Mean paired-click paradigm composite EROs (log transformed) and 95% confidence intervals for the study groups.

Table 5.7a | Paired-click paradigm composite EROs group means

Controls	EPP	
0.28 (0.03)	0.42 (0.04)	
CPP	**ARMS**	**Relatives**
0.45 (0.04)	0.22 (0.04)	0.38 (0.03)

Table 5.7b | Paired-click paradigm composite EROs between-group comparisons

Group comparisons	Est. Mean Difference	95% CI	*F* (df) p value
1. Controls Vs EPP	-0.57	-1.01 to -0.13	9.1 (4,250) $p=7.1e^{-7}$
2. Controls Vs CPP	-0.61	-1.02 to -0.19	
3. Controls Vs ARMS	0.24	-0.19 to 0.67	
4. Controls Vs Relatives	-0.25	-0.61 to 0.12	
5. EPP Vs CPP	-0.04	-0.53 to 0.44	
6. EPP Vs ARMS	0.81	0.31 to 1.31	
7. EPP Vs Relatives	0.32	-0.12 to 0.77	
8. CPP Vs ARMS	0.85	0.38 to 1.33	
9. CPP Vs Relatives	0.36	-0.05 to 0.78	
10. ARMS Vs Relatives	-0.49	-0.92 to -0.06	

Paired-click paradigm composite EROs (log transformed) mean differences between the study groups and 95% confidence intervals, adjusted for multiple comparions. EROs values were log transformed to reduce the skewness of data before ANOVA comparisons EPP - early psychosis patients; CPP - chronic psychosis patients; ARMS - 'At risk mental state' subjects.

5.8 Paired-click paradigm EROs and psychosis symptoms

EROs gating and psychosis symptoms in early psychosis

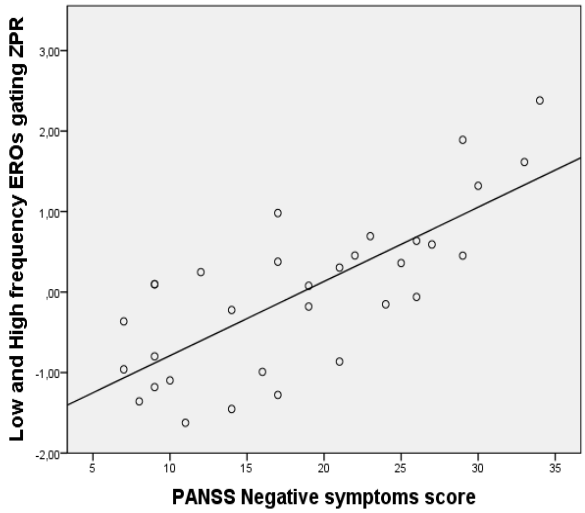


Figure 5.8 Scatter plot and fitted regression line showing the relationship between: a) low and high frequency EROs gating (Figure 5.4a) and PANSS negative symptoms scores in the early psychosis sample;

Paired-click paradigm composite EROs as extracted above were regressed with PANSS scores in the early and chronic psychosis patients samples and there were no significant associations. However, S2/S1 EROs high and low frequency clusters selected for inclusion in the composite measure (depicted in Figure 5.4a) predicted, independently, PANSS negative symptoms scores (Figure 5.8, R^2 linear=0.57, F=18.94, $p<1.0e^{-5}$, high frequency cluster: $\beta=0.49$, $t=3.95$, $p<0.001$ and low frequency cluster: $\beta=0.52$, $t=4.19$, $p<0.001$), in the early psychosis sample, but not in the chronic psychosis sample. More gating in both clusters was associated with less negative psychosis symptoms in early psychosis patients.

5.9 Paired-click paradigm composite EROs - genetic Vs chronicity effects

Results in this chapter show first-degree relatives of psychosis patients did not differ from controls nor patients in paired-click paradigm composite EROs. First-degree relatives had an intermediate group mean value between controls and patients. Paired-click paradigm composite EROs deficits were absent in the ARMS group, but present in both psychosis patients groups, with no significant difference between early and chronic patients. Together, this suggests paired-click paradigm composite EROs deficits are influenced by psychosis genetic vulnerability and psychosis onset, thereafter remaining stable over the longitudinal course of disease. This is further discussed in Chapter 7.

CHAPTER SIX

RELATIONSHIPS BETWEEN ODDBALL TASK, PASSIVE ODDBALL AND PAIRED-CLICK PARADIGMS EROS

6.0 Introduction

In this chapter, drawing from results in chapters 3, 4 and 5, EROs extracted from the oddball task, passive oddball and paired-click paradigms, are investigated with regards to their relationships, across the study groups. This is done in order to explore physiological links between the brain functions involved in each paradigm, as part of a broader attention-system and in an attempt to characterize the nature and course (genetic liability and disease effects) of neurophysiological abnormalities in psychosis. In addition, it is expected that combining EROs will produce larger differences between patients and controls, increasing the potential diagnostic aid utility of these measures. The relationships between the three paradigms EROs were investigated as the association between lower order, sensorial, brain functions measures: passive oddball and paired-click paradigms EROs and a higher order, cognitive function measure: oddball task EROs.

6.1 Relationships between oddball task, passive oddball and paired-click paradigm EROs across study groups

The ratio $\frac{\text{passive oddball paradigm EROs}}{\text{paired-click paradigm EROs}}$ predicted oddball task EROs in controls, ARMS and first-degree relatives, but not in the two psychosis patients groups, $F(1,242)=4.76$, $p<0.001$ (Table 6.1). The interaction effect remained statistically significant when only controls and patients (early and chronic psychosis groups combined) were included in the GLM univariate model, $F(1,141)=11.82$, $p<0.001$.

Table 6.1 | Associations between oddball task, passive oddball and paired-click paradigms EROs across groups

	Standardized Coefficients Beta	Std. Error	t	Sig	95% CI	
					Lower Bound	Upper Bound
Intercept	1.69	0.08	21.97	<0.001	1.54	1.84
CPP	-0.02	0.10	-0.22	0.83	-0.22	0.18
EPP	0.04	0.12	0.30	0.77	-0.20	0.27
Relatives	0.15	0.07	2.25	0.02	0.02	0.28
ARMS	0.16	0.07	2.30	0.02	0.02	0.30
Controls	0.26	0.06	4.22	<0.001	0.14	0.38

GLM univariate parameter estimates for the interaction effect: Group * ($\frac{\text{passive oddball paradigm EROs}}{\text{paired-click paradigm EROs}}$) on oddball task EROs. **EPP** - early psychosis patients; **CPP** - chronic psychosis patients; **ARMS** - 'At risk mental state' subjects.

6.2 Combined oddball task, passive oddball and paired-click paradigm EROs across study groups

The three paradigms EROs were standardized as z-scores and combined here as: oddball task EROs + passive oddball paradigm EROs - paired-click paradigm EROs. Passive oddball EROs were adjusted for age, before entering this calculation. This produces an index, "combined EROs", which would be reduced in psychosis patients, depending on their degree of impairment in all three paradigms brain functions and which reflects the relationships between these. Mean combined EROs for all the study groups are displayed in Table 6.2a. ANOVA between-group comparisons results are displayed in Table 6.2b and show a significant main effect for group: both psychosis patients groups had smaller combined EROs than controls and first-degree relatives groups. Chronic patients showed only a trend for smaller combined EROs than ARMS. There were no significant differences between controls, ARMS and first-degree relatives groups. There were no significant age, gender, smoking, nor lab main effects.

Combined oddball task, passive oddball and paired-click paradigm EROs

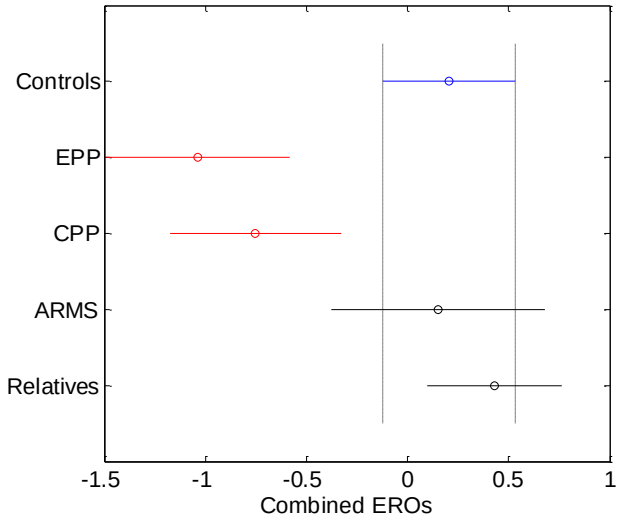


Figure 6.2a Mean three paradigms combined EROs and 95% confidence intervals for the study groups.

Table 6.2a | Three paradigms combined EROs means

Controls	EPP	
0.21 (0.17)	-1.04 (0.24)	
CPP	**ARMS**	**Relatives**
-0.75 (0.22)	0.15 (0.27)	0.43 (0.17)

Mean (se) three paradigms combined EROs for the study groups.

Table 6.2b | Three paradigms combined EROs between-group comparisons

Group comparisons	Est. Mean Difference	95% CI	*F* (df) p value
1. Controls Vs EPP	1.24	0.43 to 2.06	9.65 (4,231) p<0.0001
2. Controls Vs CPP	0.96	0.18 to 1.74	
3. Controls Vs ARMS	0.05	-0.84 to 0.95	
4. Controls Vs Relatives	-0.22	-0.90 to 0.45	
5. EPP Vs CPP	-0.28	-1.20 to 0.62	
6. EPP Vs ARMS	-1.19	-2.20 to -0.18	
7. EPP Vs Relatives	-1.47	-2.29 to -0.65	
8. CPP Vs ARMS	-0.90	-1.88 to 0.08	
9. CPP Vs Relatives	-1.18	-1.97 to -0.40	
10. ARMS Vs Relatives	-0.28	-1.18 to 0.62	

Three paradigms combined EROs mean differences between the study groups and 95% confidence intervals, adjusted for multiple comparions. **EPP** - early psychosis patients; **CPP** - chronic psychosis patients; **ARMS** - 'At risk mental state' subjects.

ROC curve for the classification of psychosis patients Vs controls, obtained from logistic regression using the subtraction: oddball task EROs - paired-click paradigm EROs (z-scores), as independent variable, is shown in Figure 6.2b. Passive oddball EROs were not included because they did not descriminate chronic psychosis patients from controls (chapter 4). The area under the curve is 0.77, with SE=0.04, 95% CI 0.70 to 0.86, at the optimum ROC point: sensitivity = 0.76 and specificity = 0.72.

Three paradigms combined EROs patients Vs controls discrimination

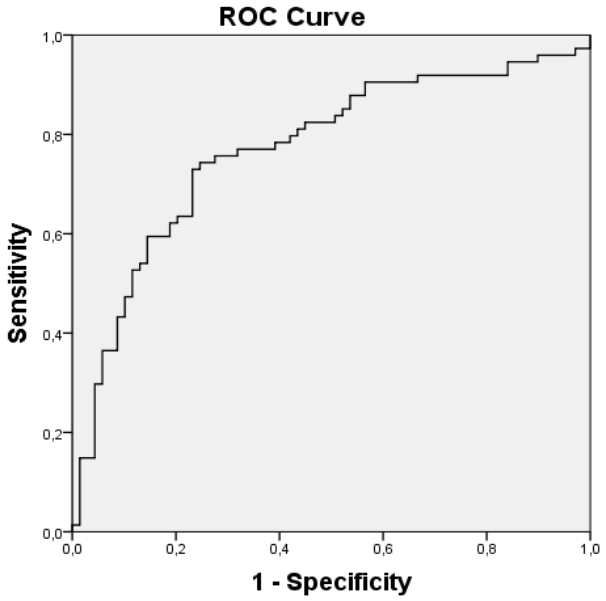


Figure 6.2b ROC curve for EROs diagnostic properties.

6.3 Combined oddball task, passive oddball and paired-click paradigm EROs as an index of psychosis disease activity

Combined oddball task, passive oddball and paired-click paradigms EROs are reduced in psychosis patients, irrespectively of whether they are at an early or chronic stage of the disease, when compared to controls and first-degree relatives. The left shift of patients groups combined EROs means in Figure 6.2a indicates a deficit in brain's overall ability to discriminate between incoming stimuli, either by attributing relevance and/or filtering irrelevant stimuli. That index could become an useful marker of psychosis active disease. Genetic liability influence and presumable brain function changes that take place during the leading period to full blown psychosis, are not directly reflected in that index, given that it did not differ between first-degree relatives, ARMS groups and controls. This is further discussed in chapter 7.

CHAPTER SEVEN

OVERALL DISCUSSION AND FUTURE DIRECTIONS

7.1 Summary and discussion of the main thesis findings

In this thesis, I set out to evaluate the functional role of brain event related oscillations from the auditory oddball task, passive oddball and paired-click paradigms, with regards to selective attention, salience attribution and sensory gating brain functions. Following this, I looked at EROs abnormalities, as potential neurophysiological markers of psychosis genetic liability and psychosis disease onset/chronicity. In this chapter, I present a summary of the main results in this thesis, their interpretation and discussion:

- Oddball task and passive oddball paradigms condition effects, when comparing target/deviant to non-target/standard tones brain EROs (Chapters 3 and 4), indicate target and deviance detection brain mechanisms depend on a pattern of increased EROs, followed by attenuated EROs, together with a fast-to-slow frequencies EROs transition. Hence, these dynamics can be used as neurophysiological markers of attention resources allocation and stimulus salience attribution. This fits with the evidence from previous studies describing similar aspects of brain function dynamics in the auditory oddball task (Fujimoto et al. 2012, Bernat *et al.* 2007,

Higashima *et al.* 2007, Mazaheri and Picton 2005, Haenschel *et al.* 2000, Traub *et al.* 1999).)

- Larger low frequency (delta and theta range) brain EROs to targets and deviant tones, when compared to non-target and standard tones, were observed over the increasing amplitude ERP slope in the two oddball paradigms (Chapters 3 and 4), likely indexing underlying excitatory neuronal activity and allocation of brain resources to target and deviant tones stimulus processing (Yordanova *et al.* 2000). Functionally, low frequency brain EROs were negatively correlated with reaction time.
- Smaller high frequency (alpha to gamma) brain EROs to targets and deviant tones, when compared to non-target and standard tones, were observed over the descending amplitude slope of the oddball paradigms ERP waveforms (Chapters 3 and 4). Conversely, larger high frequency EROs to S2 were observed when compared to S1, in relation to sensory gating (Chapter 5). High frequency brain EROs are likely to index the strength of underlying inhibitory neuronal activity (Knyazev 2007, Turrigiano and Nelson 2004, Neuper and Pfurtscheller 2001, Pfurtscheller and Lopes da Silva 1999, Yordanova *et al.* 2001, Higashima *et al.* 2007). Smaller high frequency brain EROs may be related to an increase in neuronal excitability following target and deviance detection, maximizing cortical areas prepairedness to process sensory infomation or execute motor commands; conversely, larger high frequency brain EROs, following repetitive stimuli, in the context of sensory gating, will decrease cortical excitability; accordingly, high frequency brain EROs in the two oddball paradigms were positively correlated with RT, whereas in the paired-click paradigm they were negatively correlated with RT (Chapters 3 to 5).

- Psychosis patients showed abnormal low frequency brain EROs both in the oddball task, in relation to selective attention cognitive demands, and in the paired-click paradigm, in relation to basic sensory processing (Chapters 3 and 5). This suggests that the impairment of different brain functions, at different complexity levels, occurs in psychosis through impact on brain low frequency oscillations, possibly implicating a common underlying pathophysiological mechanism (Hong et al. 2012). This may reside on brain's ability to generate low frequency oscillations, which are thought to be involved in long-range synchronization between brain areas (von Stein and Sarnthein 2000) and is impaired in schizophrenia (Uhlhaas and Singer 2012). Abnormal catecholamine and glutamate activity have been associated to disruption of brain slow oscillations and could be a potential link to psychosis (Albrecth *et al.* 2012, Hong *et al.* 2010, Ehrlichman *et al.* 2009).
- Genetic liability to psychosis induced brain EROs abnormalities in the passive oddball paradigm (Chapter 4). First-degree relatives showed increased passive oddball EROs, compared to controls and the other study groups, except chronic patients. A schizophrenia family study looking at the P3a (a salience-related ERP) also found this to be increased in first-degree relatives (Michie *et al*. 2002). Passive oddball paradigm EROs increase, in subjects who are disease-free, is suggestive of a compensatory function. A higher salience threshold or salience range, which brains use to represent the environment, may protect against irrelevant events reaching awareness ("hypersalience"), similarly to what has been proposed for MMN (Todd *et al*. 2012) and ultimately result in less presynaptic striatal dopaminergic function (Howes and Kapur 2009). That could be achieved by increasing the gain of auditory cortex neurons (Rabinowitz *et al.* 2011). A systematic review of fMRI studies in first-degree relatives supported the existence

of compensatory changes in brain function (MacDonald *et al*. 2009); moreover, compensation takes place even in the normal ageing brain (Park and Reuter-Lorenz 2009). However, further research is needed to test more fully this interpretation, as an alternative hypothesis would be that increased passive oddball EROs in fact represents an abnormal excessive brain response: "hypersalience". This alternative interpretation would require an explanation as to why did early psychosis patients show less "hypersalience" than chronic patients and their first-degree relatives, which could perhaps be attributed to medication effects. It is likely that there are also psychosis genes influences on sensory gating and oddball task paradigms EROs: first-degree relatives of psychosis patients showed no difference to controls nor patients in paired-click paradigm EROs, and their group mean value was intermediate between controls and patients; the difference between early psychosis patients and first-degree relatives oddball task EROs did not reach statistical significance, although there was a trend. These interpretations are, however, weakened by the lack of statistically significant differences between relatives and controls and the effects are only inferred from the pattern of means in controls, relatives and patients.

Of note, theta-alpha frequency brain EROs gating has been shown impaired in schizophrenia patients first-degree relatives (Hong *et al.* 2008) and reduced attenuation of oddball tasks parietal alpha power has also been shown in adolescents at familial risk for schizophrenia (Kayser *et al.* 2014, Donkers *et al.* 2011). That is in keeping with previous reports of P50 ratio and P300 deficits associated with psychosis genetic liability (see introduction).

- Transition from ARMS to psychosis (the onset of psychosis) was linked to impairment in sensory gating EROs and these brain EROs were predictive of

patients' symptoms in early psychosis (Chapter 5). The impairment of sensory gating, added upon a brain inability to increase its salience range (Chapter 4), may mark, in succession, the onset of psychosis. The onset of psychosis has previously been linked to deficient ERPs gating (van Tricht *et al*. 2012, Hsieh *et al*. 2012) and deficient activity of inhibitory cortical networks (Hasan *et al.* 2012).

- Psychosis chronicity, as assessed by comparing brain function in early Vs chronic psychosis patients, was associated with an increase in passive oddball EROs, after adjustment for age (Chapter 4). With psychosis progression, the dependence of psychosis symptoms on brain EROs also changed from sensory gating to passive oddball EROs (Chapters 4 and 5). Studies using various investigation modalities have described brain functional and structural compensatory adaptations in schizophrenia, involving namely working memory and executive function networks (Faget-Agius *et al*. 2013, Koike *et al*. 2013, Barr *et al*. 2010, De Vico Fallani *et al*. 2010, Minzenberg *et al*. 2009, Tan *et al*. 2007, Kindermann *et al*. 2004). Genetic expression patterns in the prefrontal cortex of schizophrenic subjects change from the early to chronic stages (Narayan *et al.* 2008). More broadly, adaptive changes in brain function could contribute to maintain neuropsychological performance, in the face of progressive neuroanatomical abnormalities in schizophrenia (Cobia *et al*. 2012) and it is worth noting different subgroups of patients may follow different cognitive trajectories (Thompson *et al*. 2013), based for instance on the severity of psychosis primary deficits and available brain plasticity. Similarly to what has been shown for the P300 ERP (see introduction), increasing deficits in oddball task EROs may also occur with psychosis disease chronicity, because although early and chronic psychosis patients showed no statistically significant difference, the former

group unlike the latter did not reach a significant difference to the ARMs group (Chapter 3).

❖ Figure 7.1 depicts a tentative model of changes in the studied auditory attention-related brain EROs, along the psychosis stages.

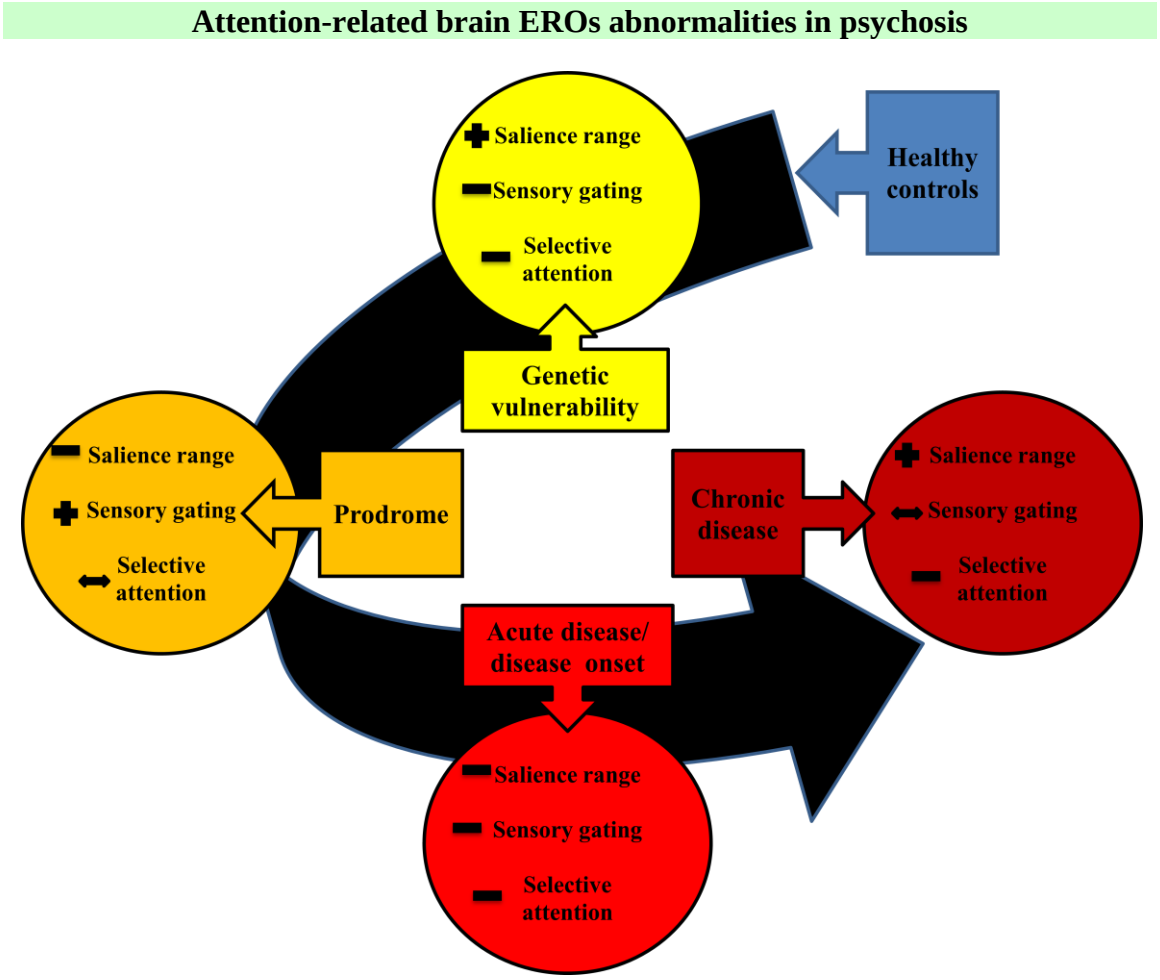


Figure 7.1 + indicates increase, - indicates loss, ↔ indicates no change, compared to the preceding stage. Salience range, sensory gating and selective attention brain functions are interpreted as reflected respectively by passive oddball, sensory gating and oddball task EROs.

❖ Combining standardized brain EROs from the three studied paradigms (oddball task + passive oddball - sensory gating EROs z-scores), showed that psychosis patients, but not first-degree relatives nor ARMS subjects, differed from controls in the overall balance between the studied brain functions (Chapter 6). This is compatible with the existence of compensatory brain changes in first-degree relatives and

ARMS groups, that maintain brain function within normal boundaries and consequently keep those subjects assymptomatic, despite psychosis genes influence or premorbid changes in brain function. Accordingly, first-degree relatives had an increased salience range in comparison with healthy controls (Chapter 4), whereas ARMS subjects had increased sensory gating strength compared to what would have been expected based on their psychosis genetic loading (Chapter 5). A relative increase in sensory gating could be adaptive in stimuli rich environments, however it could be detrimental for the appraisal of stimuli with low contrast, for example during sensory deprivation, where there is evidence of an increase in psychotic-like experiences in psychotic-prone individuals (Mason and Brady 2009). Sensory gating and salience brain functions may show a functional anti-correlated balance (Wyatt and Machado 2013), in feeding sensorial information to selective attention. The combined brain EROs ratio integrates influences on attention-related brain functions, from psychosis genetic liability, psychosis onset and progression, as well as brain compensatory effects. The combined brain EROs ratio can be interpreted as an overall index of psychosis disease expression and allostatic adaptations in the brain.

- Assessing the relationships between the three studied paradigms shows an association between lower order, sensorial, brain functions measures: passive oddball and sensory gating EROs; and a higher order, cognitive function measure: oddball task EROs. These physiological links are disrupted in psychosis patients (Chapter 6). These relationships have been shown to be bidirectional: auditory stimulus novelty attribution recruits attention and vice versa, attention enhances auditory cortex responses to targets; brain gating/inhibitory mechanisms are involved in the formation of auditory sensory memory and also in top down

attentional control (Shinn-Cunningham 2008, Fritz *et al*. 2007, Jaaskelainen *et al*. 2007, Ulanovsky *et al*. 2003, Melara *et al.* 2002). Psychosis patients' lack of integration between these brain functions could reflect poor connectivity between central hubs of the brain (Van den Heuvel *et al*. 2013, Nestor *et al*. 2007).

- As reviewed above, the studied brain EROs showed mixed genetic and disease progression influences, which supports disease models that attempt to reconcile genetic and neurodegenerative theories, where genetic vulnerability and developmental insults, are interwoven with substance use, stress, dysregulation of HPA axis function and glutamate neurotoxicity, amongst other etiopathogenic factors (Stone *et al*. 2007, Pantelis *et al*. 2003, Keshavan 1999, Woods 1998).
- On the whole, the studied brain EROs were more robust measures of psychosis disease expression than the respective paradigm's ERP, namely against the confounding effects of gender, age or lab. Unlike MMN and P50 ratio abnormalities which were found linked to psychosis in this study, P300 amplitude deficits (Bramon *et al*. 2004) were not replicated. This could be due to a number of factors: the use of a less stringent approach to EEG data inclusion, compared to other studies where some participants data was rejected based on ERP visual inspection criteria (Turetsky *et al.* 2015); the patients that were tested in this study were as a group and based on their mean PANSS scores, not very symptomatic (Leucht *et al.* 2005), making the state dimension of P300 amplitude less altered (Mathalon *et al.* 2000); unmeasured confounders could have affected P300 amplitude in controls, like ethnicity and drugs use (Turetsky *et al.* 2015).
- Medication, in particular antipsychotics, could have influenced the measured brain EROs (Koch *et al*. 2015). Our study design, by comparing early to chronic psychosis patients, partly controls for that influence, because the two patients

samples were medicated, thus reducing the likelihood that differences between the two groups are due to medication effects. However, it cannot be ruled out the possibility that potential antipsychotics effects on brain EROs increased over time, given brain structure alterations were found to be correlated with cumulative exposure to antipsychotic treatments (Fusar-Poli *et al*. 2013). That would produce stronger effects in chronic, compared to early psychosis patients. But if indeed medication was to have a progressive effect on the studied brain EROs, then this would not be equal across them: whereas passive oddball EROs differed between early psychosis and chronic psychosis patients, paired-click paradigm EROs did not. Also of note, antipsychotic effects could not explain the brain EROs differences found between ARMS, first-degree relatives or controls (e.g: first-degree relatives had larger passive oddball paradigm EROs than ARMS and controls), given none of these groups were medicated. Previous studies on brain EROs in schizophrenia have found deficits that were independent of medication status, by comparing unmedicated to medicated patients and controls (Sun *et al*. 2013, Minzenberg *et al*. 2010, Gallinat *et al*. 2004) and which were genetically determined, by looking at monozygotic twin pairs discordant for schizophrenia (Hall *et al*. 2011). Similar study designs could be used in the, future looking at the studied brain EROs, in order to elucidate potential medication effects.

- There are other limitations to this study: it would be necessary to track brain event related oscillations longitudinally, on cohorts of subjects identified based on risk factors as more prone to develop psychosis, from early childhood, through onset and years of duration of disease, in order to provide unequivocal evidence of brain EROs genetic, developmental as well as progressive changes in psychosis. Only one electrode per paradigm was analyzed in this study, hence topographical effects

and brain sources were not investigated; this approach, however, minimized the problem of multiple comparisons and facilitates future translation to clinical application by making data collection/analysis simpler.

7.2 Conclusions and future directions

This thesis brings insights into brain physiological mechanisms underlying selective attention resources allocation, stimuli salience attribution, sensory gating and the specific abnormalities in those dynamics that are associated to psychosis disease and its symptoms. It also sheds light on the impact of psychosis vulnerability genes and psychosis disease progression on brain function and how the brain might develop compensatory adaptations. This knowledge could have impact on the wider psychosis research field. Further work, beyond the scope of this thesis, could be undertaken on the study sample investigated here and/or a larger sample, by including subjects from whom colleagues have retrieved more data. There would be value in examining brain EROs topographical effects and exploring other types of metrics, including EEG source and connectivity analysis. It would be most interesting to bridge the gap between brain function measures described here and candidate genes for psychosis. As discussed earlier, studies with different designs are needed to fully disentangle genetic and progressive disease influences on brain function. Studies designed to test the ability of the EROs measures developed in this thesis in predicting prognosis and response to treatment could give evidence for their direct clinical applicability. With the same end in mind, studying EROs in samples of different psychiatric populations could reveal diagnostic utility. Finally, the understanding of the functional role of EROs in the studied paradigms could lead to applications outside the clinical remit and be used for example to assess brain function in healthy subjects whilst performing tasks in work or leisure environments. It is hoped that this thesis contributes to the advance in this field of research and that this may translate into clinical applications that ultimately will improve patients lives.

CHAPTER EIGHT

PAPERS

At the time of submission of this thesis, I have submitted two papers for publication, as first-author, based on the content of this PhD thesis. The two papers are included in this chapter.

PAPER 1

Title Page

Word count (body of text): 3412

Word count (abstract): 250

Tables: 2

Figures: 3 composite pictures

Title: Neurophysiological signals of genetic liability, disease onset and progression in psychosis

Miguel Constante[1,3], Nicolas A. Crossley[3], Madiha Shaikh[3], Robin M Murray[3], Elvira Bramon[2].

[1] Hospital Beatriz Ângelo, Lisbon, Portugal.

[2] Division of Psychiatry & Institute of Cognitive Neuroscience, University College London, UK.

[3] Department of Psychosis Studies, Institute of Psychiatry, King's College London.

Key words: schizophrenia; EEG; event related oscillations; P300; P50; MMN.

*Corresponding author: Dr Miguel Constante, Hospital Beatriz Ângelo, Departamento de Psiquiatria e Saúde Mental, Avenida Carlos Teixeira nº3, 2674-514 Loures, Portugal.

Email address: miguel.constante@kcl.ac.uk).

ABSTRACT

BACKGROUND: Event-Related Oscillations (EROs) have been linked to cognition and found to be abnormal in psychotic disorders. It is unclear if EROs deficits reflect genetic liability to psychosis, the onset and/or progression of psychosis disease.

METHODS: 35 early psychosis and 44 chronic psychosis patients, 69 unaffected first-degree relatives, 40 subjects with 'at risk mental state' (ARMS) and 76 healthy controls were included in this study. Subjects underwent electroencephalography recording during an auditory oddball task, a duration-deviant passive oddball paradigm, and a paired-click paradigm, which elicit selective attention, salience detection and sensory gating brain processes respectively. Wavelet-based time-frequency analyses were conducted to extract single trial EROs. Relevant EROs were identified by examining EROs condition effects, EROs associations with reaction time and EROs differences between patients and controls, through cluster-based t-tests and regression analysis. EROs were compared between groups using ANOVA, regressed to test relationships between the three paradigms and associations with psychosis symptoms scores.

RESULTS: Selective attention EROs were influenced by psychosis disease progression, salience EROs by disease chronicity and sensory gating EROs by disease onset. The three EROs types were also influenced by psychosis genetic liability. Psychosis symptoms were predicted by sensory gating and salience EROs in early and chronic patients, respectively. Stronger salience and gating EROs combined predicted stronger selective attention EROs in all groups, except in psychosis patients. First-degree relatives and ARMS subjects showed evidence of EROs compensatory changes.

CONCLUSIONS: In psychosis, attention-related EROs reflect genetic vulnerability, disease onset and progression, together with brain compensatory adaptations and ageing.

INTRODUCTION

Schizophrenia is a chronic severe mental illness leading to impaired cognition and functioning. The neurodevelopmental model posits that it is the outcome of abnormalities in maturational processes caused by genetic and environmental factors (1-3). The Kraepelin model, on the other hand, emphasizes neurodegenerative changes, taking place after disease onset, resulting in gradual decline of cognitive and social functioning (4). Brain function abnormalities which are stable over time, presenting even before the onset of schizophrenia, could reflect genetic liability and be used as endophenotypes (5), whereas biomarkers correlating with psychosis severity could be valuable in its clinical staging, providing insights into treatment and prognosis (6, 7). Event related oscillations (EROs) mediate sensory, cognitive processes (8) and are affected in schizophrenia (9-13). Different EROs time-frequencies reflect distinct brain functions and may be impaired by different disease mechanisms, therefore measuring and integrating multiple EROs is necessary in order to unravel schizophrenia complex neurophysiological abnormalities (9-14). There are well established neurophysiological impairments in schizophrenia, elicited by the auditory oddball task (15-17), passive oddball (16, 18-21) and paired-click gating paradigms (16, 22-24), from which the P300, mismatch negativity (MMN) event related potentials and P50/N100 gating are traditionally measured. These paradigms involve different brain functions: the oddball task is linked to cognitive information processing, including memory, attention and executive functions (25, 26); the passive oddball produces an involuntary attention-call signal to auditory change (27); the paired-click paradigm elicits sensory gating, testing the brain's ability to filter incoming irrelevant stimuli and focus attention (28). Fewer studies have looked at these paradigms' EROs and their abnormalities in schizophrenia: chronic schizophrenia patients had deficits in oddball task delta and theta EROs, that were associated with decreased P300 amplitude, (29-31); dependence of MMN on theta band oscillations was shown in healthy subjects (32) and using the same paradigm, theta-alpha range oscillations were abnormally enhanced in chronic schizophrenia patients (33); in the sensory gating paradigm, EROs reductions in theta/alpha (34, 35) and beta (36) bands contributed to decreased P50 or N100 gating in schizophrenia patients.

Preliminary evidence shows that EROs tap onto psychosis genetic vulnerability: the early auditory evoked gamma-band response (37-39) and theta-alpha frequency EROs gating (40) were found abnormal both in schizophrenia patients and in their first-degree relatives. Although there is evidence of psychosis progression effects on P300, MMN and P50 ratio (41-51), this has not yet been investigated for the respective paradigms EROs, to our knowledge. It is also unknown if EROs from the oddball task, passive oddball and gating paradigms are related, even if a few studies have linked their ERPs (52-54). Arguably, the attention system and its key mechanism of salience detection (55), a core element of schizophrenia etiopathogenesis (56), is a common factor modulating brain's reactions across the oddball task (57), passive oddball (58) and sensory gating paradigms (59-61). Moreover, combining different neurophysiological paradigms on the same sample of patients can provide complementary information, helping to characterize the population more accurately (62, 63).

The main aims of this study were to investigate the neurophysiology of attention-related auditory EROs and how these are affected by psychosis genetic liability, disease onset and progression. We hypothesized that genetically linked EROs abnormalities would be present in first-degree relatives. We hypothesized that the onset and progression of psychosis, from ARMS, through early psychosis to chronic psychosis, would be associated with increasing EROs abnormalities.

METHODS AND MATERIALS

Participants

We used a cross-sectional design comparing 5 groups: an early psychosis sample, 35 individuals between 18-35 years old with a DSM-IV diagnosis of a psychotic disorder with an onset of psychotic symptoms less than 5 years previously; a sample of 44 chronic patients diagnosed with schizophrenia or schizoaffective disorder; a ARMS sample of 40 subjects with an "at risk mental state" (ARMS), according to criteria established by Yung and colleagues (64); a sample of 69 first-degree relatives of psychosis patients; another sample of 76 controls without a personal or family history of psychotic disorder. Most participants (controls, ARMS and early

psychosis patients) were recruited individually, however a part of the chronic patients and relatives groups were recruited for a family study (21, 43): of the 264 participants, 181 (68.6%) were singletons, 58 (22.0%) were part of families with two members in the study, 21 (8,0%) were in three-person families, and 4 (1.5%) were in one four-person family. A history of neurological disorders, head injury with loss of consciousness longer than a couple of minutes or a DSM-IV diagnosis of alcohol or illegal substance dependence in the 12 months prior to assessment were exclusion criteria across all the subjects groups. Demographic and clinical data are summarized in table 1. All participants gave written informed consent to enter the study. This research was approved by the Ethical Committee at the Institute of Psychiatry.

Table 2.1a | Clinical and demographic characteristics of overall sample

Group		Controls	First-degree relatives	Psychosis patients	ARMS	
N		76	69	79	40	
♀ : ♂ (% Male)[a]		34 :35 (54%)	41 : 28 (41%)	20 : 59 (75%)**	16 : 24 (60%)	χ^2 (3) = 18.1, p<0.001
Mean Age (SD)[b]		34.6 (14.0)	52.0 (15.8)***	34.1 (12.1)	24.2 (4.2)**	F (3,252) = 40.4, p<0.001
Tobacco[2] – Non-Smokers : Smokers (% Smokers)[c]		66 : 10 (13%)	49 : 18 (27%)*	27 : 51 (65%)***	11 : 18 (62%)***	χ^2 (3) = 54.9, p<0.001
DSM-IV Diagnosis		No Psychiatric Disorder (73) Major depression (1) Minor depression (2)	No Psychiatric Disorder (42) Major depression without psychotic features (21) Anxiety disorder (4) Cyclotymic disorder (1)	Schizophrenia (57) Schizoaffective Disorder (7) Bipolar Disorder, type 1 (7) Schizophreniform Disorder (3) Acute and transient psychotic disorder (3) Major depressive disorder, with psychotic symptoms (1)	No Psychiatric Disorder (12) Depressive disorder (6) Substance misuse (5) Anxiety disorder (3) Personality disorder (2) Personality disorder and depression (2)	
Positive And Negative Symptoms Scale[3]	**Positive (SD)**	-	-	11.2 (4.4)		
	Negative (SD)	-	-	16.5 (8.1)		
	General (SD)	-	-	27.8 (8.5)		
	Total (SD)	-	-	55.6 (18.0)		

[a] Significant gender differences were found between the study groups: the psychosis patients group had more males than the controls group. [b] There were significant age differences between the study groups: relatives were older and ARMS subjects were younger than controls. [c] There were smoking status differences between the study groups: first-degree relatives, psychosis patients and ARMS subjects groups included more smokers than the controls group. *,** and *** indicate significant differences from control group at $p<0.05$, $p<0.01$, $p<0.001$ respectively.

Tasks, EEG recordings and EROs measurements

EEG data was recorded using a 40-channel electrode cap positioned according to the 10/20 International System referenced to linked mastoids and grounded at Fpz, with all electrode impedances kept at under 5kΩ. Data was continuously digitised at 1000 Hz with a digital 0.1-100 Hz band pass filter (24 dB/octave roll-off). The continuous EEG was segmented offline into large epochs time-locked to auditory stimuli (–3100 to 2500 ms), in order to allow analysis of low frequency bands and minimize edge effects. Artefact rejection was performed to reject data segments containing eye blinks, muscle artefacts and amplitudes exceeding +/- 100 μV. Line noise removal was performed at 50Hz using a discrete Fourier transform.

Data were registered while subjects performed 3 experiments, in this order: auditory oddball task, passive oddball and paired-click paradigms. Their duration was approximately 15, 6 and 20-25 minutes, respectively. The oddball task (65) consisted of one block of four hundred tones, with a 2 second (±0.2 second) inter-stimulus interval, 80% of the tones were 'non-targets' of 1000 Hz and 20% were 'targets' of 1500 Hz. Subjects were instructed to a press a button with their preferred hand when identifying a target. Reaction time (RT) was measured as the median button press response latency to target tones, in milliseconds and response accuracy was calculated as the percentage of correctly identified targets. The passive oddball paradigm (21) consisted of three blocks of 400 stimuli (0.3 sec inter-stimulus interval) with 85% standards (25 ms, 1000 Hz, 5-ms rise/fall time) and 15% duration deviants (50 ms duration, 5 ms rise/fall time). Tones had an intensity of 80dB in both tasks. Finally, four or five blocks of 30 pairs of conditioning (S1) and test (S2) clicks were obtained (66), with stimulus adjusted individually to 43 dB above the hearing threshold. S1 and S2 were of 1 ms duration and separated by 500 ms. Intertrial intervals between click pairs were 10 seconds. Subjects were requested not to smoke at least 30 minutes before data collection (67).

Time-frequency analyses from single trials were performed using Morlet wavelets with a 'width' of 4 (12), power was extracted with a 1 Hz (frequency) and 1 msec (time) resolution for baseline and post-stimuli intervals. The EEG frequency bands of interest were Delta (1-3Hz), Theta (4-7Hz), Alpha (8-12Hz), Beta (13-30Hz) and Gamma (31-100Hz). For EROs calculation, relative

baseline correction (the quotient of post stimuli power over baseline average power) was applied and baseline lengths were determined separately for each band: Delta (-1000 to 0 ms), Theta (-250 to 0 ms), Alpha (-125 to 0 ms), Beta (-100 to 0 ms), Gamma (-50 to 0 ms). Hence, EROs represent the post-stimuli relative change of power in comparison to the baseline.

EROs of interest were those with a functional link to: a) task (condition) effects; or b) behavioural performance, as measured by oddball task reaction time (RT); or that would c) discriminate between patients and controls. To identify these EROs, t-test comparisons were performed between each paradigm's two stimuli EROs time-frequency spectrums (Figures 1a-c), between controls and patients (Figure 1g-h) and EROs time-frequency spectrums were regressed with RT and PANSS scores (Figures 1d-f), creating time-frequency maps with clusters of statistically significant t-test scores and regression coefficients (68). These clusters were mapped onto target tone, deviant tone and S2/S1 EROs time-frequency spectrums, to delimitate EROs of interest. Composite EROs ratios were calculated for each paradigm, by combining EROs across frequencies, following the same rational as others investigating EEG markers of attention and cognition (69-76). The aim was to make composite EROs measures reflect psychosis impairments in: 1) isolated EROs time-frequency clusters; and/or 2) EROs "collective behaviour", as ensembles of EROs time-frequency clusters that are functionally linked in each studied paradigm. This approach allows to establish functional links between different EROs and thus integrate different brain processes, as argued by various authors (9-12).

EROs were extracted from each paradigm as follows: *Oddball-task-EROs* - from the target tone EROs spectrum, a ratio was calculated between EROs mapped taking maximum values from the positive and negative clusters in Figure 1d: $\left(\frac{negative\ clusters\ EROs}{positive\ cluster\ EROs}\right)$; this ratio was weighed (multiplied) by the maximum EROs value within the boundaries defined by the delta/theta cluster in Figure 1g. *Passive-oddball-EROs* - from the deviant tone EROs spectrum, a ratio was calculated between maximum EROs values mapped by the positive and negative clusters in Figure 1b: $\left(\frac{positive\ clusters\ EROs}{negative\ cluster\ EROs}\right)$. *Paired-click-EROs*: S2/S1 EROs spectrum was computed;

from this, a ratio was calculated between maximum S2/S1 values mapped by the positive and negative clusters in Figure 1f: $\left(\frac{positive\ cluster\ EROs}{negative\ clusters\ EROs}\right)$; this ratio was weighed (multiplied) by the minimum S2/S1 EROs value within the boundaries defined by the theta cluster in Figure 1h. These EROs were combined between all 3 paradigms in one index (c_EROs), after being converted into standardized z-scores, as: oddball-task-EROs + passive-oddball-EROs - paired-click-EROs. Passive-oddball-EROs were adjusted for age, before entering this calculation.

ANOVA, including gender and age as covariates, was conducted for each individual paradigm extracted EROs and c_EROs; EROs correlations within families were controlled for by use of a random effect. Extreme outliers (3xIQR below 1st quartile or above 3rd quartile, totalling less than 3 subjects/group) were excluded. A significant ANOVA overall test was followed up by multiple pairwise comparisons, with tukey-kramer correction for experiment-wise error rate. Another univariate linear model with an interaction term: clinical group * $\frac{\text{passive−oddball−EROs}}{\text{sensory−EROs−gating}}$, as independent variable and oddball-task-EROs as dependent variable, was used to test the relationship between lower level and higher level EROs across study groups. The three paradigms EROs were introduced together in regression analysis to predict PANSS positive and negative symptoms scores in early and chronic patients groups separately.

RESULTS

Behavioural results

Mean target tone response accuracy and RT for each study group are displayed in table 1. There were no statistically significant group differences for target tone response accuracy. There was a group effect on RT, ($F(4,260) = 6.83$, $p<0.0001$), controls were faster than early psychosis patients (Δ = -117ms, 95% CI = -182 to -52ms) and chronic psychosis patients (Δ = -68ms, 95% CI = -129 to -7ms), but showed no difference to ARMS nor first-degree relatives groups. Men had faster RT than women, $F(1,260) = 12.24$, $p<0.001$, Δ = -49ms, 95% CI = -78 to -19ms.

Time-frequency analysis by test condition and associations with reaction time

The condition effects (tone types comparisons) for the 3 studied paradigms in the overall study sample (all subjects combined) are shown in Figures 1a-c t-test scores. Oddball task target tones elicited larger EROs in the delta/theta frequency range and in the late gamma range, but smaller alpha EROs than non-target tones (Figure 1a). Linear regression coefficients in Figure 1d show a negative cluster associating target tone early gamma/delta/theta EROs with RT. Conversely, later target tone gamma, alpha/beta EROs clusters were positively associated with RT. As such, smaller early gamma/low frequency EROs and larger late alpha/beta EROs were markers of slower RT. Passive oddball deviant tones elicited larger early gamma and delta/theta EROs, but smaller late beta EROs than standard tones (Figure 1b). Linear regression coefficients in Figure 1e show the association between patients' deviant minus standard tone EROs difference and RT; as that difference increases in an early gamma and theta frequency windows, RT is faster and as that difference is smaller in a late beta frequency window, RT is slower. In the paired-click paradigm, S1 elicited larger delta/theta EROs but smaller gamma EROs than S2 (Figure 1c). Linear regression coefficients in Figure 1f show the association between patients' S2/S1 EROs ratio and RT; smaller S2/S1 low frequency EROs ratio is linked to slower RT, whereas larger S2/S1 high frequency EROs ratio is linked to faster RT.

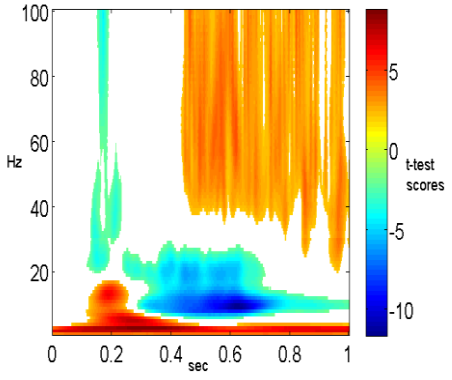
Controls Vs patients EROs spectrums comparisons

In the oddball task, t-test scores in Figure 1g show reduced target tone delta/theta EROs in patients compared to controls. In the passive oddball paradigm, deviant tones EROs spectrums did not differ between patients and controls. Controls showed smaller S2/S1 theta EROs ratios (meaning stronger gating) than patients, as indicated by t-test scores in Figure 1h.

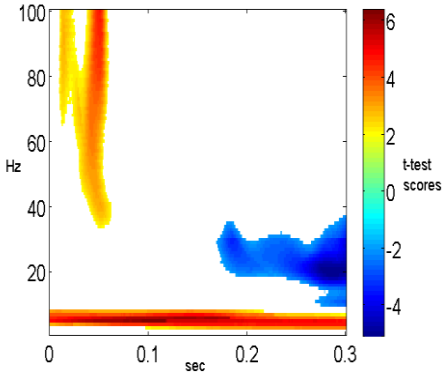
Figure 1

EROs condition effects across all subjects

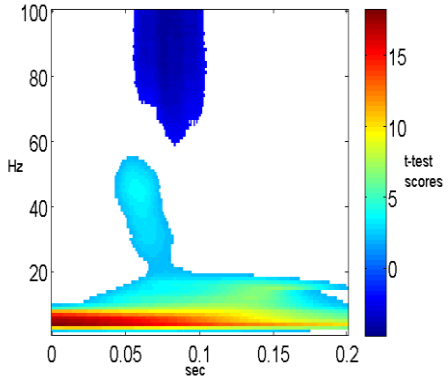
a) Oddball task target Vs non-target tone EROs (Pz)



b) Passive oddball paradigm deviant Vs standard tone EROs (Fz)

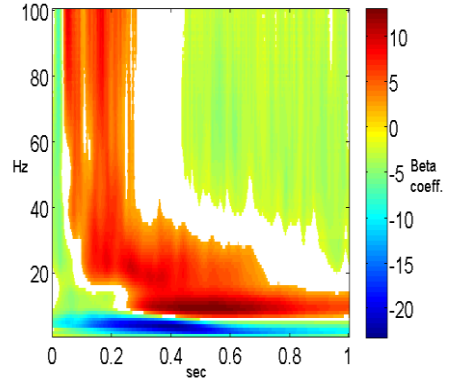


c) Paired-click paradigm S1 Vs S2 tone EROs (Cz)

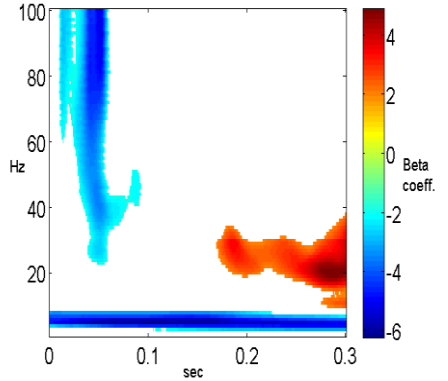


EROs relationships with reaction time (RT)

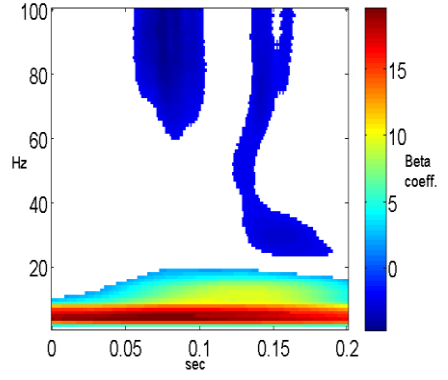
d) Oddball task target tone EROs and RT



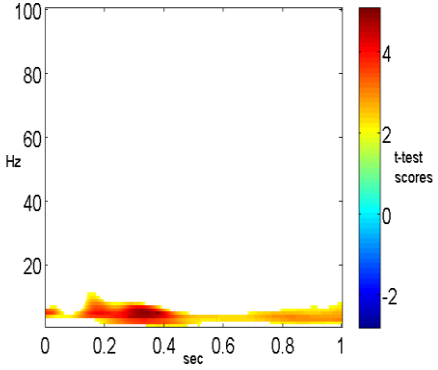
e) Passive oddball deviant-standard tone EROs difference and RT



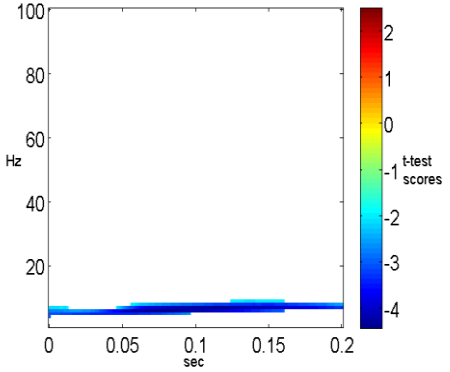
f) Paired-click paradigm EROs gating and RT



g) Oddball task target tone EROs: controls Vs patients



h) Paired-click paradigm EROs gating: controls Vs patients



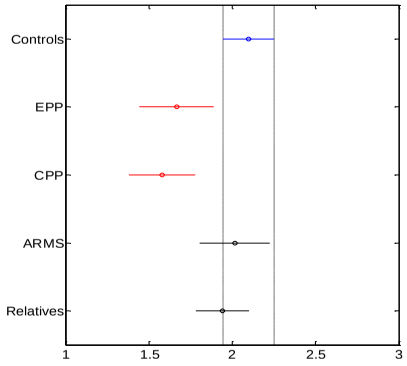
a) t-test scores for comparisons between oddball task target Vs non-target tones EROs spectrums, at Pz electrode. **b)** t-test scores for comparisons between passive oddball paradigm deviant Vs standard tones EROs spectrums, at Fz electrode. **c)** t-test scores for comparisons between paired-click paradigm S1 Vs S2 tones EROs spectrums, at Cz electrode. **d)** Linear regression coefficients for the associations between oddball task target tone EROs and RT. **e)** Linear regression coefficients for the associations between passive oddball paradigm EROs difference (deviant-standard) and RT. **f)** Linear regression coefficients for the associations between paired-click paradigm S2/S1 EROs ratio and RT. All study subjects were included in analyses from pictures 1a-1f. **g)** t-test scores for comparisons between controls Vs patients oddball task target tone EROs spectrums. **h)** t-test scores for comparisons between controls Vs patients paired-click paradigm S2/S1 EROs ratio. EEG frequency is indicated on the y-axis, time is indicated on the x-axis and zero denotes the occurrence of stimuli. T-test scores (1a-1c and 1g-h) or Beta coefficients (1d-1f) are indicated on a colour scale located to the far right of each plot. All results are adjusted for multiple comparisons and a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$.

Results of between-group comparisons for extracted EROs are displayed in Figure 2. We found significant group effects on oddball-task-EROs, $F(4,260)=5.45$, $p=3.0e^{-4}$, passive-oddball-EROs, $F(4,246)=4.7$, $p=0.001$, paired-click-EROs, $F(4,250)=9.10$, $p=7.1e^{-7}$ and c_EROs, $F(4,230)=9.65$, $p=3.2e^{-7}$. Passive-oddball-EROs decreased with increasing age in the overall sample ($F(1,246)=9.35$, $p=0.002$, $\beta=-0.16$). Gender had no effect on any of the studied paradigms extracted EROs. On post-hoc pairwise comparisons (Figure 2 sub-tables), controls showed larger oddball-task-EROs than early psychosis patients and chronic psychosis patients, but no significant difference to ARMS or relatives groups. ARMS subjects showed larger oddball-task-EROs than chronic psychosis patients, but not early psychosis patients. There was a trend for larger passive-oddball-EROs in controls, compared to early psychosis patients. First-degree relatives showed larger passive-oddball-EROs than controls, early psychosis patients and ARMS groups, but no significant difference to chronic psychosis patients. Early psychosis patients showed smaller passive-oddball-EROs than chronic psychosis patients but no significant difference to the ARMS group. Controls had stronger paired-click-EROs than early and chronic psychosis patients. ARMS subjects had stronger gating than early psychosis patients, chronic psychosis patients and first-degree relatives. The latter group gating mean was intermediate between controls and patients, but did not statistically differ from them. Both psychosis patients groups, but not ARMS nor first-degree relatives had smaller combined EROs than controls.

Scatter plots in Figures 2e-f, with fitted regression lines, show the relationship between paired-click-EROs, passive-oddball-EROs and negative psychosis symptoms in early psychosis (R^2 linear=0.57, r= 0.66, $p<0.0001$) and chronic psychosis (R^2 linear=0.21, r= 0.46, $p<0.01$) patients, respectively. No significant association was found between extracted EROs and PANSS positive symptoms scores.

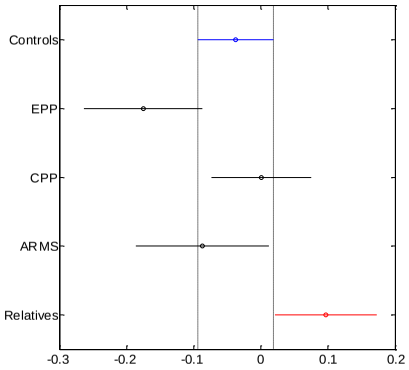
Figure 2.

a) Oddball-task-EROs



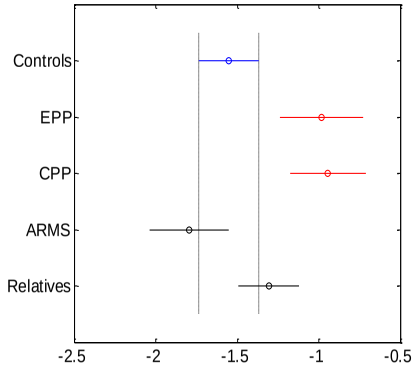
Group comparisons	Est. Mean Difference	95% CI
1. Cs Vs EPP	0.43	0.06 to 0.81
2. Cs Vs CPP	0.52	0.17 to 0.87
3. Cs Vs ARMS	0.08	-0.28 to 0.45
4. Cs Vs Rs	0.16	-0.15 to 0.46
5. EPP Vs CPP	0.09	-0.33 to 0.51
6. EPP Vs ARMS	-0.35	-0.78 to 0.08
7. EPP Vs Rs	-0.28	-0.66 to 0.11
8. CPP Vs ARMS	-0.44	-0.85 to -0.03
9. CPP Vs Rs	-0.36	-0.72 to -0.004
10. ARMS Vs Rs	-0.07	-0.30 to 0.44

b) Passive-oddball-EROs



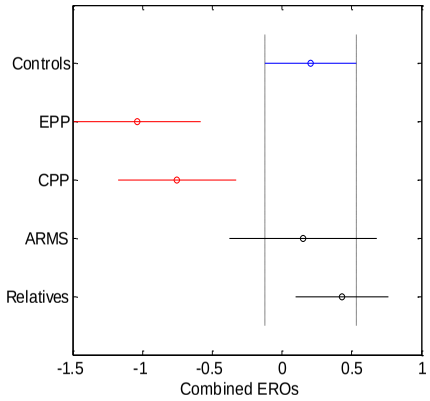
Est. Mean Difference	95% CI
0.14	-0.006 to 0.28
-0.04	-0.17 to 0.09
0.05	-0.11 to 0.20
-0.13	-0.26 to -0.004
-0.18	-0.34 to -0.008
-0.09	-0.26 to 0.08
-0.27	-0.44 to -0.10
-0.09	-0.09 to 0.27
-0.10	-0.23 to 0.04
-0.18	-0.18 to -0.00005

c) Paired-click-EROs



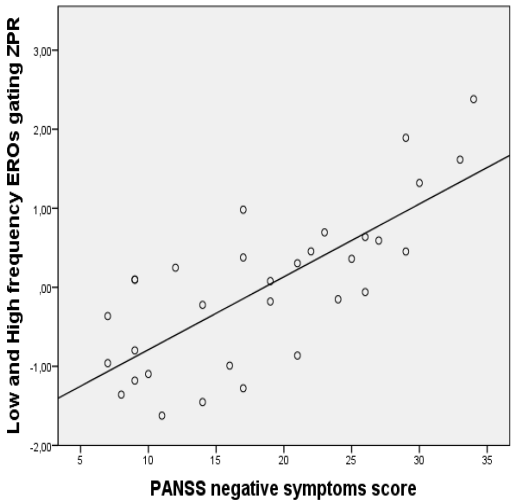
Est. Mean Difference	95% CI
-0.57	-1.01 to -0.13
-0.61	-1.02 to -0.19
0.24	-0.19 to 0.67
-0.25	-0.61 to 0.12
-0.04	-0.53 to 0.44
0.81	0.31 to 1.31
0.32	-0.12 to 0.77
0.85	0.38 to 1.33
0.36	-0.05 to 0.78
-0.49	-0.92 to -0.06

d) Attention, salience, sensory gating EROs combined

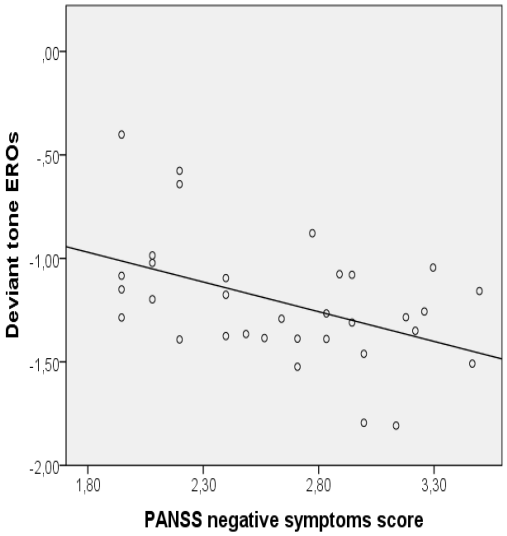


Group comparisons	Est. Mean Difference	95% CI
1. Cs Vs EPP	1.24	0.43 to 2.06
2. Cs Vs CPP	0.96	0.18 to 1.74
3. Cs Vs ARMS	0.05	-0.84 to 0.95
4. Cs Vs Rs	-0.22	-0.90 to 0.45
5. EPP Vs CPP	-0.28	-1.20 to 0.62
6. EPP Vs ARMS	-1.19	-2.20 to -0.18
7. EPP Vs Rs	-1.47	-2.29 to -0.65
8. CPP Vs ARMS	-0.90	-1.88 to 0.08
9. CPP Vs Rs	-1.18	-1.97 to -0.40
10. ARMS Vs Rs	-0.28	-1.18 to 0.62

e) EROs and symptoms in early psychosis



f) EROs and symptoms in chronic psychosis



a) to d) study groups oddball-task-EROs, passive-oddball-EROs, paired-click-EROs and combined EROs estimated means and 95% confidence intervals, respectively. Passive-oddball-EROs are adjusted for age. EROs in a) to c) have been log transformed. **e)** scatter plot and fitted regression line showing the relationship between low and high frequency paired-click-EROs as independent variables and PANSS negative symptoms score in EPP; regression standardized predicted values (ZPR) are indicated on the y-axis and symptoms scores on the x-axis; **f)** scatter plot and fitted regression line showing the relationship between passive-oddball-EROs and PANSS negative symptoms score in CPP; **Cs** - Controls; **EPP** - Early psychosis patients; **CPP** - Chronic psychosis patients; **ARMS** - 'At risk mental state' subjects; **Rs** - First-degree relatives.

Relationship between oddball task, passive oddball and sensory gating EROs

The ratio $\frac{\text{passive oddball paradigm EROs}}{\text{sensory gating paradigm EROs}}$ predicted oddball task EROs in controls, ARMS and first-degree relatives, but not in the two psychosis patients groups, $F(1,242)=4.76$, $p<0.001$ (Table 2). The interaction effect remained statistically significant when only controls and patients (early and chronic psychosis groups combined) were included in the GLM univariate model, $F(1,141)=11.82$, $p<0.001$.

Table 2. Associations between oddball task, passive oddball and sensory gating paradigms EROs across groups

	Standardized Coefficients Beta	Std. Error	t	Sig	95% CI	
					Lower Bound	Upper Bound
Intercept	1.69	0.08	21.97	<0.001	1.54	1.84
CPP	-0.02	0.10	-0.22	0.83	-0.22	0.18
EPP	0.04	0.12	0.30	0.77	-0.20	0.27
Relatives	0.15	0.07	2.25	0.02	0.02	0.28
ARMS	0.16	0.07	2.30	0.02	0.02	0.30
Controls	0.26	0.06	4.22	<0.001	0.14	0.38

GLM univariate parameter estimates for the interaction effect Group*($\frac{\text{passive-oddball-EROs}}{\text{sensory-EROs-gating}}$) ratio on oddball task EROs. **EPP** - early psychosis patients; **CPP** - chronic psychosis patients; **ARMS** - 'At risk mental state' subjects.

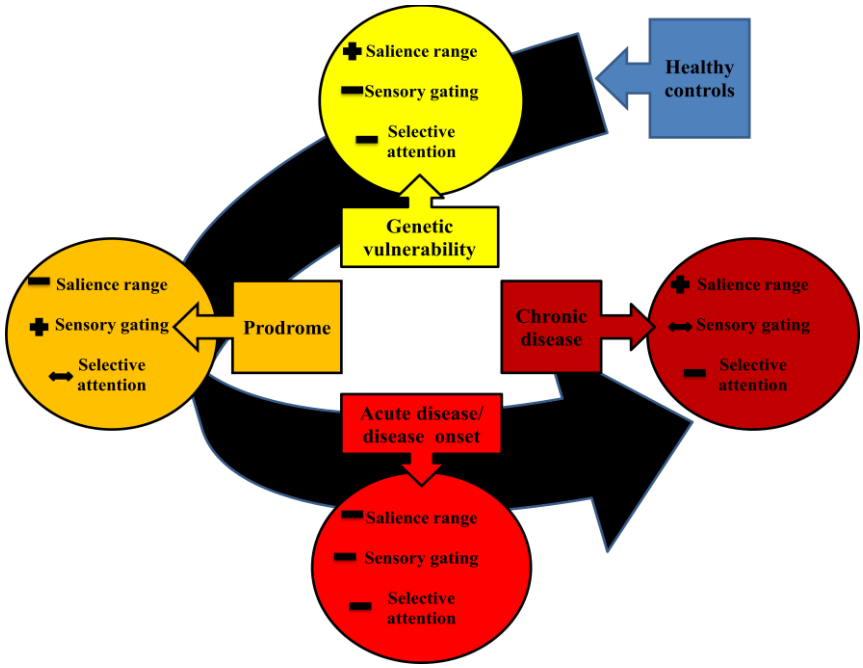
DISCUSSION

In this study, we have looked at auditory event related oscillatory power across different tasks, with a view to differentiating brain function profiles at different stages of the psychosis spectrum and psychosis genetic liability. We identified EROs markers of selective attention, salience and sensory gating brain responses, measured from the oddball task, passive oddball and paired-click paradigms, respectively. The three paradigms EROs were linked, except in the psychosis patients groups, where this link was disrupted (table 2), possibly reflecting poor functional connectivity between central hubs of the brain (77, 78). The links between the studied paradigms EROs are likely bidirectional: auditory stimulus novelty attribution recruits attention and vice versa, attention enhances auditory cortex responses to targets; brain gating/inhibitory mechanisms are involved in the formation of auditory sensory memory and also in top down attentional control (79-83).

Our results indicate oddball-task-EROs may be reduced by psychosis genetic liability, disease onset and progression altogether, making oddball-task-EROs a marker of overall psychosis deficits. Oddball-task-EROs were impaired following psychosis disease onset (patients compared to controls); they appeared to deteriorate over the longitudinal course of the disease, given chronic psychosis patients, unlike early psychosis patients, differed from the ARMS group; and also be reduced by genetic influence, given the difference between early psychosis patients and first-degree relatives also did not reach statistical significance (Figure 2a). Our results revealed increased salience EROs in first-degree relatives of psychosis patients (Figure 2b). Similarly, a schizophrenia family study looking at the P3a found this to be increased in first-degree relatives (84). The salience EROs increase, in disease-free subjects, is suggestive of compensatory brain activity, which could be achieved through an increase in the gain of auditory cortex neurons (85). A systematic review of fMRI studies in first-degree relatives supported the existence of compensatory changes in brain function (86); in fact, compensation exists even in the normal ageing brain (87). Early psychosis and ARMS subjects had smaller salience EROs compared to first-degree relatives, indicating a failure to develop and/or the breakdown of that compensatory brain activity. A lower salience threshold/range, with which brains represent the environment, may result in irrelevant events reaching awareness more often ("hypersalience"), similarly to what has been proposed for MMN (58), and ultimately increased presynaptic striatal dopaminergic function (88). Following from the above, passive-oddball-EROs might prove valuable as a proxy measure of psychosis genetic loading in first-degree relatives and as a means to assessing brain function (de)compensation status in patients. In addition, because passive-oddball-EROs decrease with ageing in our overall sample, they may index cognitive decline and deficient *N*-methyl-d-aspartate (NMDA) receptor functioning, likewise MMN (89). It would be expected for ARMS subjects to show, as a group, psychosis genes associated deficits in brain function (90, 91), however, we found instead that paired-click-EROs were stronger in ARMS subjects compared to first-degree relatives (Figure 2c). Whereas first-degree relatives brains could increase salience EROs to compensate for the genetic influence on oddball-task EROs, ARMS subjects brains could compensate that by increasing

sensory gating. Paired-click-EROs and passive-oddball-EROs may show a physiological balance (92), that could keep first-degree relatives and ARMS subjects' attention system functioning within normal limits. The loss of sensory gating compensation may constitute a second "hit" to brain function and mark the transition from the prodrome to psychosis (Figure 2c). In this respect, paired-click-EROs could become a useful biomarker of transition to psychosis. This transition has previously been linked to deficient ERPs gating (93, 94) and deficient activity of inhibitory cortical networks (95). In this study, progression from an early to chronic psychosis stage, led to larger age-adjusted salience EROs in patients (Figure 2b) and psychosis symptoms dependence on these EROs, rather than paired-click-EROs (Figures 2e-f). Brain functional and structural adaptations in schizophrenia, involving namely working memory and executive function networks, have been shown using various investigation modalities (96-102). Genetic expression patterns in the prefrontal cortex of schizophrenic subjects change from the early to chronic stages (103). More broadly, adaptive changes in brain function could contribute to maintain neuropsychological performance, in the face of progressive neuroanatomical abnormalities in schizophrenia (104). Figure 3 represents a summary model of attention-related EROs changes associated to psychosis.

Figure 3. Attention-related EROs abnormalities in psychosis



Because the studied EROs showed multiple psychosis associated influences, our results support disease models that attempt to reconcile genetic and neurodegenerative theories, where genetic vulnerability and progressive developmental insults, are interwoven with substance use, stress, dysregulation of HPA axis function and glutamate neurotoxicity, amongst other etiopathogenic factors (105-109).

This study has limitations, which include the fact that we used a cross sectional design, whereas longitudinal within-subject studies following up patients from as early as before the prodromal stage and long after disease onset, would provide stronger evidence of genetic and/or disease influences on brain function. We did not control for medication effects, nor correct for the number of statistical comparisons in all the analyses, treating each paradigm independently.

In conclusion, in psychosis attention-related neurophysiological markers are influenced by genetic vulnerability, disease onset and progression, as well as brain compensatory adaptations and ageing.

ACKNOWLEDGEMENTS

The authors would like to thank all participants who took part in this research. We thank also the following organizations for their support: Hospital Beatriz Ângelo and Dr. Maria João Heitor for providing M Constante with research time. E Bramon has held a Medical Research Council (MRC) New Investigator Award and a MRC Centenary Award. Further support to E Bramon was provided by the National Institute of Health Research UK (post-doctoral fellowship), the Brain and Behavior Research foundation's (two NARSAD's Young Investigator Awards) and a Wellcome Trust Research Training Fellowship. N Crossley was supported by the Wellcome Trust. This project was also funded by the Psychiatry Research Trust, the Schizophrenia Research Fund and The Wellcome Trust.

DECLARATION OF INTEREST

The authors report no competing interest.

REFERENCES

1. Rapoport, J. L., J. N. Giedd and N. Gogtay (2012). "Neurodevelopmental model of schizophrenia: update 2012." Mol Psychiatry **17**(12): 1228-1238.
2. Murray, R. M. and S. W. Lewis (1987). "Is schizophrenia a neurodevelopmental disorder?" Br Med J (Clin Res Ed). **295**(6600): 681-682.
3. Weinberger, D. R. (1987). "Implications of normal brain development for the pathogenesis of schizophrenia." Arch Gen Psychiatry. **44**(7): 660-669.
4. Lieberman, J. A. (1999). "Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective." Biological Psychiatry **46**(6): 729-739.
5. Gottesman, II and T. D. Gould (2003). "The endophenotype concept in psychiatry: etymology and strategic intentions." Am J Psychiatry **160**(4): 636-645.
6. Light, G. A., N. R. Swerdlow, A. J. Rissling, A. Radant, C. A. Sugar, J. Sprock, M. Pela, M. A. Geyer and D. L. Braff (2012). "Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia." PLoS One **7**(7): e39434.
7. Luck, S. J., D. H. Mathalon, B. F. O'Donnell, M. S. Hamalainen, K. M. Spencer, D. C. Javitt and P. J. Uhlhaas (2011). "A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research." Biol Psychiatry **70**(1): 28-34.
8. Basar, E., C. Basar-Eroglu, S. Karakas and M. Schurmann (2001). "Gamma, alpha, delta, and theta oscillations govern cognitive processes." Int J Psychophysiol **39**(2-3): 241-248.
9. Basar, E. (2013). "Brain oscillations in neuropsychiatric disease." Dialogues Clin Neurosci 15(3): 291-300.
10. Buzsaki, G. and B. O. Watson (2012). "Brain rhythms and neural syntax: implications for efficient coding of cognitive content and neuropsychiatric disease." Dialogues Clin Neurosci **14**(4): 345-367.
11. Moran, L. V. and L. E. Hong (2011). "High vs low frequency neural oscillations in schizophrenia." Schizophr Bull **37**(4): 659-663.
12. Uhlhaas, P. J. and W. Singer (2010). "Abnormal neural oscillations and synchrony in schizophrenia." Nat Rev Neurosci **11**(2): 100-113.
13. Roach, B. J. and D. H. Mathalon (2008). "Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia." Schizophr Bull 34(5): 907-926.
14. van der Stelt, O. and A. Belger (2007). "Application of electroencephalography to the study of cognitive and brain functions in schizophrenia." Schizophr Bull 33(4): 955-970.
15. Turetsky, B. I., E. M. Dress, D. L. Braff, M. E. Calkins, M. F. Green, T. A. Greenwood, R. E. Gur, R. C. Gur, L. C. Lazzeroni, K. H. Nuechterlein, A. D. Radant, L. J. Seidman, L. J. Siever, J. M. Silverman, J. Sprock, W. S. Stone, C. A. Sugar, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang and G. Light (2015). "The utility of P300 as a schizophrenia endophenotype and predictive biomarker: Clinical and socio-demographic modulators in COGS-2." Schizophr Res **163**(1-3): 53-62.
16. Bramon, E., S. Rabe-Hesketh, P. Sham, R. M. Murray and S. Frangou (2004). "Meta-analysis of the P300 and P50 waveforms in schizophrenia." Schizophr Res **70**(2-3): 315-329.
17. Light, G. A., N. R. Swerdlow, M. L. Thomas, M. E. Calkins, M. F. Green, T. A. Greenwood, R. E. Gur, R. C. Gur, L. C. Lazzeroni, K. H. Nuechterlein, M. Pela, A. D. Radant, L. J. Seidman, R. F. Sharp, L. J. Siever, J. M. Silverman, J. Sprock, W. S. Stone, C. A. Sugar, D. W. Tsuang, M. T. Tsuang, D. L. Braff and B. I. Turetsky (2015). "Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: Characterization of demographic, clinical, cognitive, and functional correlates in COGS-2." Schizophr Res **163**(1-3): 63-72.
18. Naatanen, R. and S. Kahkonen (2009). "Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review." Int J Neuropsychopharmacol **12**(1): 125-135.
19. Umbricht, D. and S. Krljes (2005). "Mismatch negativity in schizophrenia: a meta-analysis." Schizophr Res **76**(1): 1-23.
20. Bramon, E., R. J. Croft, C. McDonald, G. K. Virdi, J. G. Gruzelier, T. Baldeweg, P. C. Sham, S. Frangou and R. M. Murray (2004). "Mismatch negativity in schizophrenia: a family study." Schizophr Res **67**(1): 1-10.
21. Olincy, A., D. L. Braff, L. E. Adler, K. S. Cadenhead, M. E. Calkins, D. J. Dobie et al (2010). "Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the Consortium on Genetics of Schizophrenia." Schizophr Res **119**(1-3): 175-182.
22. Boutros, N. N., A. Brockhaus-Dumke, K. Gjini, A. Vedeniapin, M. Elfakhani, S. Burroughs and M. Keshavan (2009). "Sensory-gating deficit of the N100 mid-latency auditory evoked potential in medicated schizophrenia patients." Schizophr Res **113**(2-3): 339-346.
23. Patterson, J. V., W. P. Hetrick, N. N. Boutros, Y. Jin, C. Sandman, H. Stern, S. Potkin and W. E. Bunney, Jr. (2008). "P50 sensory gating ratios in schizophrenics and controls: a review and data analysis." Psychiatry Res **158**(2): 226-247.
24. Turetsky, B. I., M. E. Calkins, G. A. Light, A. Olincy, A. D. Radant and N. R. Swerdlow (2007). "Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures." Schizophr Bull **33**(1): 69-94.
25. Polich, J. (2007). "Updating P300: an integrative theory of P3a and P3b." Clin Neurophysiol 118(10): 2128-2148.
26. Sutton, S., M. Braren, J. Zubin and E. R. John (1965). "Evoked-potential correlates of stimulus uncertainty." Science **150**(3700): 1187-1188.
27. Naatanen, R., T. Kujala and I. Winkler (2011). "Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses." Psychophysiology **48**(1): 4-22.
28. Freedman, R., M. Waldo, P. Bickford-Wimer and H. Nagamoto (1991). "Elementary neuronal dysfunctions in schizophrenia." Schizophr Res **4**(2): 233-243.

29. Doege, K., A. T. Bates, T. P. White, D. Das, M. P. Boks and P. F. Liddle (2009). "Reduced event-related low frequency EEG activity in schizophrenia during an auditory oddball task." Psychophysiology **4**6(3): 566-577.
30. Ford, J. M., B. J. Roach, R. S. Hoffman and D. H. Mathalon (2008). "The dependence of P300 amplitude on gamma synchrony breaks down in schizophrenia." Brain Res 1235: 133-142.
31. Roschke, J. and J. Fell (1997). "Spectral analysis of P300 generation in depression and schizophrenia." Neuropsychobiology 35(2): 108-114.
32. Fuentemilla, L., J. Marco-Pallares, T. F. Munte and C. Grau (2008). "Theta EEG oscillatory activity and auditory change detection." Brain Res 1220: 93-101.
33. Elliot Hong, L., L. V. Moran, X. Du, P. O'Donnell and A. Summerfelt (2012). "Mismatch negativity and low frequency oscillations in schizophrenia families." Clin Neurophysiol 123(10): 1980-1988.
34. Brockhaus-Dumke, A., R. Mueller, U. Faigle and J. Klosterkoetter (2008). "Sensory gating revisited: relation between brain oscillations and auditory evoked potentials in schizophrenia." Schizophr Res 99(1-3): 238-249.
35. Jansen, B. H., A. Hegde and N. N. Boutros (2004). "Contribution of different EEG frequencies to auditory evoked potential abnormalities in schizophrenia." Clin Neurophysiol 115(3): 523-533.
36. Hong, L. E., A. Summerfelt, R. P. McMahon, G. K. Thaker and R. W. Buchanan (2004). "Gamma/beta oscillation and sensory gating deficit in schizophrenia." Neuroreport 15(1): 155-159.
37. Leicht, G., V. Kirsch, I. Giegling, S. Karch, I. Hantschk, H. J. Moller, O. Pogarell, U. Hegerl, D. Rujescu and C. Mulert (2010). "Reduced early auditory evoked gamma-band response in patients with schizophrenia." Biol Psychiatry 67(3): 224-231.
38. Leicht, G., S. Karch, E. Karamatskos, I. Giegling, H. J. Moller, U. Hegerl, O. Pogarell, D. Rujescu and C. Mulert (2011). "Alterations of the early auditory evoked gamma-band response in first-degree relatives of patients with schizophrenia: hints to a new intermediate phenotype." J Psychiatr Res 45(5): 699-705.
39. Hall, M. H., G. Taylor, P. Sham, K. Schulze, F. Rijsdijk, M. Picchioni, T. Toulopoulou, U. Ettinger, E. Bramon, R. M. Murray and D. F. Salisbury (2011). "The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia." Schizophr Bull 37(4): 778-787.
40. Hong, L. E., A. Summerfelt, B. D. Mitchell, R. P. McMahon, I. Wonodi, R. W. Buchanan and G. K. Thaker (2008). "Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate." Arch Gen Psychiatry 65(9): 1008-1016.
41. van der Stelt, O., J. A. Lieberman and A. Belger (2005). "Auditory P300 in high-risk, recent-onset and chronic schizophrenia." Schizophr Res **77**(2-3): 309-320.
42. Brown, K. J., C. J. Gonsalvez, A. W. Harris, L. M. Williams and E. Gordon (2002). "Target and non-target ERP disturbances in first episode vs. chronic schizophrenia." Clin Neurophysiol **113**(11): 1754-1763.
43. Bramon, E., C. McDonald, R. J. Croft, S. Landau, F. Filbey, J. H. Gruzelier, P. C. Sham, S. Frangou and R. M. Murray (2005). "Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study." Neuroimage **27**(4): 960-968.
44. Ozgurdal, S., Y. Gudlowski, H. Witthaus, W. Kawohl, I. Uhl, M. Hauser, I. Gorynia, J. Gallinat, M. Heinze, A. Heinz and G. Juckel (2008). "Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia." Schizophr Res **105**(1-3): 272-278.
45. Mathalon, D. H., J. M. Ford and A. Pfefferbaum (2000). "Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study." Biol Psychiatry **47**(5): 434-449.
46. Jahshan, C., K. S. Cadenhead, A. J. Rissling, K. Kirihara, D. L. Braff and G. A. Light (2012). "Automatic sensory information processing abnormalities across the illness course of schizophrenia." Psychol Med **42**(1): 85-97.
47. Magno, E., S. Yeap, J. H. Thakore, H. Garavan, P. De Sanctis and J. J. Foxe (2008). "Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia." Biol Psychiatry **64**(5): 385-391.
48. Brockhaus-Dumke, A., I. Tendolkar, R. Pukrop, F. Schultze-Lutter, J. Klosterkotter and S. Ruhrmann (2005). "Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia." Schizophr Res **73**(2-3): 297-310.
49. Salisbury, D. F., N. Kuroki, K. Kasai, M. E. Shenton and R. W. McCarley (2007). "Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia." Arch Gen Psychiatry **64**(5): 521-529.
50. Umbricht, D. S., J. A. Bates, J. A. Lieberman, J. M. Kane and D. C. Javitt (2006). "Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia." Biol Psychiatry **59**(8): 762-772.
51. Brockhaus-Dumke, A., F. Schultze-Lutter, R. Mueller, I. Tendolkar, A. Bechdolf, R. Pukrop, J. Klosterkoetter and S. Ruhrmann (2008). "Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients." Biol Psychiatry **64**(5): 376-384.
52. Gjini, K., C. Arfken and N. N. Boutros (2010). "Relationships between sensory "gating out" and sensory "gating in" of auditory evoked potentials in schizophrenia: a pilot study." Schizophr Res 121(1-3): 139-145.
53. Leitman, D. I., P. Sehatpour, B. A. Higgins, J. J. Foxe, G. Silipo and D. C. Javitt (2010). "Sensory deficits and distributed hierarchical dysfunction in schizophrenia." Am J Psychiatry 167(7): 818-827.
54. Kisley, M. A., T. L. Noecker and P. M. Guinther (2004). "Comparison of sensory gating to mismatch negativity and self-reported perceptual phenomena in healthy adults." Psychophysiology 41(4): 604-612.
55. Corbetta, M. and G. L. Shulman (2002). "Control of goal-directed and stimulus-driven attention in the brain." Nat Rev Neurosci **3**(3): 201-215.
56. Kapur, S. (2003). "Psychosis as a state of aberrant salience: a framework linking biology,

phenomenology, and pharmacology in schizophrenia." Am J Psychiatry **160**(1): 13-23.
57. Coull, J. T. (1998). "Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology." Prog Neurobiol **55**(4): 343-361.
58. Todd, J., P. T. Michie, U. Schall, P. B. Ward and S. V. Catts (2012). "Mismatch negativity (MMN) reduction in schizophrenia-impaired prediction--error generation, estimation or salience?" Int J Psychophysiol **83**(2): 222-231.
59. Smith, A. K., J. C. Edgar, M. Huang, B. Y. Lu, R. J. Thoma, F. M. Hanlon, G. McHaffie, A. P. Jones, R. D. Paz, G. A. Miller and J. M. Canive (2010). "Cognitive abilities and 50- and 100-msec paired-click processes in schizophrenia." Am J Psychiatry **167**(10): 1264-1275.
60. Rosburg, T., P. Trautner, C. E. Elger and M. Kurthen (2009). "Attention effects on sensory gating--intracranial and scalp recordings." Neuroimage **48**(3): 554-563.
61. Potter, D., A. Summerfelt, J. Gold and R. W. Buchanan (2006). "Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia." Schizophr Bull **32**(4): 692-700.
62. Turetsky, B. I., W. B. Bilker, S. J. Siegel, C. G. Kohler and R. E. Gur (2009). "Profile of auditory information-processing deficits in schizophrenia." Psychiatry Res **165**(1-2): 27-37.
63. Price, G. W., P. T. Michie, J. Johnston, H. Innes-Brown, A. Kent, P. Clissa and A. V. Jablensky (2006). "A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia." Biol Psychiatry **60**(1): 1-10.
64. Yung, A. R., H. P. Yuen, P. D. McGorry, L. J. Phillips, D. Kelly, M. Dell'Olio, S. M. Francey, E. M. Cosgrave, E. Killackey, C. Stanford, K. Godfrey and J. Buckby (2005). "Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States." Aust N Z J Psychiatry **39**(11-12): 964-971.
65. Schulze, K. K., M. H. Hall, C. McDonald, N. Marshall, M. Walshe, R. M. Murray and E. Bramon (2008). "Auditory P300 in patients with bipolar disorder and their unaffected relatives." Bipolar Disord **10**(3): 377-386.
66. Schulze, K. K., M. H. Hall, C. McDonald, N. Marshall, M. Walshe, R. M. Murray and E. Bramon (2007). "P50 auditory evoked potential suppression in bipolar disorder patients with psychotic features and their unaffected relatives." Biol Psychiatry **62**(2): 121-128.
67. Adler, L. E., L. D. Hoffer, A. Wiser and R. Freedman (1993). "Normalization of auditory physiology by cigarette smoking in schizophrenic patients." Am J Psychiatry **150**(12): 1856-1861.
68. Gross, J. (2014). "Analytical methods and experimental approaches for electrophysiological studies of brain oscillations." J Neurosci Methods **228**: 57-66.
69. Schleiger, E., N. Sheikh, T. Rowland, A. Wong, S. Read and S. Finnigan (2014). "Frontal EEG delta/alpha ratio and screening for post-stroke cognitive deficits: the power of four electrodes." Int J Psychophysiol **94**(1): 19-24.
70. Sangal, R. B. and J. M. Sangal (2014). "Use of EEG Beta-1 Power and Theta/Beta Ratio Over Broca's Area to confirm Diagnosis of Attention Deficit/Hyperactivity Disorder in Children." Clin EEG Neurosci.
71. Putman, P., B. Verkuil, E. Arias-Garcia, I. Pantazi and C. van Schie (2014). "EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention." Cogn Affect Behav Neurosci **14**(2): 782-791.
72. Moretti, D. V., D. Paternico, G. Binetti, O. Zanetti and G. B. Frisoni (2014). "EEG upper/low alpha frequency power ratio and the impulsive disorders network in subjects with mild cognitive impairment." Curr Alzheimer Res **11**(2): 192-199.
73. Staikou, C., A. Kyrozis, C. Moschovos and A. Fassoulaki (2012). "Effects of morning melatonin administration on electroencephalographic theta to alpha power ratio in reproductive versus postmenopausal healthy female volunteers." Neurosci Lett **507**(1): 90-93.
74. Ogrim, G., J. Kropotov and K. Hestad (2012). "The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: sensitivity, specificity, and behavioral correlates." Psychiatry Res **198**(3): 482-488.
75. Leon-Carrion, J., J. F. Martin-Rodriguez, J. Damas-Lopez, J. M. Barroso y Martin and M. R. Dominguez-Morales (2009). "Delta-alpha ratio correlates with level of recovery after neurorehabilitation in patients with acquired brain injury." Clin Neurophysiol **120**(6): 1039-1045.
76. Barry, R. J., A. R. Clarke, S. J. Johnstone, R. McCarthy and M. Selikowitz (2009). "Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes." Biol Psychiatry **66**(4): 398-401.
77. van den Heuvel, M. P., O. Sporns, G. Collin, T. Scheewe, R. C. Mandl, W. Cahn, J. Goni, H. E. Hulshoff Pol and R. S. Kahn (2013). "Abnormal rich club organization and functional brain dynamics in schizophrenia." JAMA Psychiatry **70**(8): 783-792.
78. Nestor, P. G., M. Kubicki, K. M. Spencer, M. Niznikiewicz, R. W. McCarley and M. E. Shenton (2007). "Attentional networks and cingulum bundle in chronic schizophrenia." Schizophr Res **90**(1-3): 308-315.
79. Shinn-Cunningham, B. G. (2008). "Object-based auditory and visual attention." Trends Cogn Sci. **12**(5): 182-186. doi: 110.1016/j.tics.2008.1002.1003. Epub 2008 Apr 1017.
80. Fritz, J. B., M. Elhilali, S. V. David and S. A. Shamma (2007). "Auditory attention--focusing the searchlight on sound." Curr Opin Neurobiol. **17**(4): 437-455. Epub 2007 Aug 2021.
81. Jaaskelainen, I. P., J. Ahveninen, J. W. Belliveau, T. Raij and M. Sams (2007). "Short-term plasticity in auditory cognition." Trends Neurosci. **30**(12): 653-661. Epub 2007 Nov 2005.
82. Ulanovsky, N., L. Las and I. Nelken (2003). "Processing of low-probability sounds by cortical neurons." Nat Neurosci. **6**(4): 391-398.
83. Melara, R. D., A. Rao and Y. Tong (2002). "The duality of selection: excitatory and inhibitory

processes in auditory selective attention." J Exp Psychol Hum Percept Perform. **28**(2): 279-306.
84. Michie, P. T., H. Innes-Brown, J. Todd and A. V. Jablensky (2002). "Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders." Biol Psychiatry **52**(7): 749-758.
85. Rabinowitz, N. C., B. D. Willmore, J. W. Schnupp and A. J. King (2011). "Contrast gain control in auditory cortex." Neuron. **70**(6): 1178-1191. doi: 1110.1016/j.neuron.2011.1104.1030.
86. MacDonald, A. W., 3rd, H. W. Thermenos, D. M. Barch and L. J. Seidman (2009). "Imaging genetic liability to schizophrenia: systematic review of FMRI studies of patients' nonpsychotic relatives." Schizophr Bull. **35**(6): 1142-1162. doi: 1110.1093/schbul/sbn1053. Epub 2008 Jun 1112.
87. Park, D. C. and P. Reuter-Lorenz (2009). "The adaptive brain: aging and neurocognitive scaffolding." Annu Rev Psychol **60:173-96.**(doi): 10.1146/annurev.psych.1159.103006.093656.
88. Howes, O. D. and S. Kapur (2009). "The dopamine hypothesis of schizophrenia: version III--the final common pathway." Schizophr Bull **35**(3): 549-562.
89. Naatanen, R., T. Kujala, C. Escera, T. Baldeweg, K. Kreegipuu, S. Carlson and C. Ponton (2012). "The mismatch negativity (MMN)--a unique window to disturbed central auditory processing in ageing and different clinical conditions." Clin Neurophysiol **123**(3): 424-458.
90. Cannon, T. D., T. G. van Erp, C. E. Bearden, R. Loewy, P. Thompson, A. W. Toga, M. O. Huttunen, M. S. Keshavan, L. J. Seidman and M. T. Tsuang (2003). "Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions." Schizophr Bull **29**(4): 653-669.
91. Lawrie, S. M., H. C. Whalley, S. S. Abukmeil, J. N. Kestelman, L. Donnelly, P. Miller, J. J. Best, D. G. Owens and E. C. Johnstone (2001). "Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia." Biol Psychiatry. **49**(10): 811-823.
92. Wyatt, N. and L. Machado (2013). "Evidence inhibition responds reactively to the salience of distracting information during focused attention." PLoS One. **8**(4): e62809. doi: 62810.61371/journal.pone.0062809. Print 0062013.
93. van Tricht, M. J., D. H. Nieman, J. T. Koelman, A. J. Mensink, L. J. Bour, J. N. van der Meer, T. A. van Amelsvoort, D. H. Linszen and L. de Haan (2012). "Sensory gating in subjects at ultra high risk for developing a psychosis before and after a first psychotic episode." World J Biol Psychiatry **26**: 26.
94. Hsieh, M. H., J. C. Shan, W. L. Huang, W. C. Cheng, M. J. Chiu, F. S. Jaw, H. G. Hwu and C. C. Liu (2012). "Auditory event-related potential of subjects with suspected pre-psychotic state and first-episode psychosis." Schizophr Res. **140**(1-3): 243-249. doi: 210.1016/j.schres.2012.1006.1021. Epub 2012 Jul 1010.
95. Hasan, A., T. Wobrock, C. Grefkes, M. Labusga, K. Levold, T. Schneider-Axmann, P. Falkai, H. Muller, J. Klosterkotter and A. Bechdolf (2012). "Deficient inhibitory cortical networks in antipsychotic-naive subjects at risk of developing first-episode psychosis and first-episode schizophrenia patients: a cross-sectional study." Biol Psychiatry. **72**(9): 744-751. doi: 710.1016/j.biopsych.2012.1003.1005. Epub 2012 Apr 1012.
96. Faget-Agius, C., L. Boyer, C. Lancon, R. Richieri, E. Fassio, E. Soulier, V. Chanoine, P. Auquier, J. P. Ranjeva and M. Guye (2013). "Structural and functional reorganization of working memory system during the first decade in schizophrenia. A cross-sectional study." Schizophr Res. **151**(1-3): 48-60. doi: 10.1016/j.schres.2013.1010.1023. Epub 2013 Nov 1011.
97. Koike, S., R. Takizawa, Y. Nishimura, M. Kinou, S. Kawasaki and K. Kasai (2013). "Reduced but broader prefrontal activity in patients with schizophrenia during n-back working memory tasks: a multi-channel near-infrared spectroscopy study." J Psychiatr Res. **47**(9): 1240-1246. doi: 1210.1016/j.jpsychires.2013.1205.1009. Epub 2013 Jun 1243.
98. Barr, M. S., F. Farzan, L. C. Tran, R. Chen, P. B. Fitzgerald and Z. J. Daskalakis (2010). "Evidence for excessive frontal evoked gamma oscillatory activity in schizophrenia during working memory." Schizophr Res. **121**(1-3): 146-152. doi: 110.1016/j.schres.2010.1005.1023. Epub 2010 Jul 1013.
99. De Vico Fallani, F., A. Maglione, F. Babiloni, D. Mattia, L. Astolfi, G. Vecchiato, A. De Rinaldis, S. Salinari, E. Pachou and S. Micheloyannis (2010). "Cortical network analysis in patients affected by schizophrenia." Brain Topogr. **23**(2): 214-220. doi: 210.1007/s10548-10010-10133-10542. Epub 12010 Jan 10522.
100. Minzenberg, M. J., A. R. Laird, S. Thelen, C. S. Carter and D. C. Glahn (2009). "Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia." Arch Gen Psychiatry **66**(8): 811-822.
101. Tan, H. Y., J. H. Callicott and D. R. Weinberger (2007). "Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia." Cereb Cortex. **17**(Suppl 1): i171-181.
102. Kindermann, S. S., G. G. Brown, L. E. Zorrilla, R. K. Olsen and D. V. Jeste (2004). "Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI." Schizophr Res. **68**(2-3): 203-216.
103. Narayan, S., B. Tang, S. R. Head, T. J. Gilmartin, J. G. Sutcliffe, B. Dean and E. A. Thomas (2008). "Molecular profiles of schizophrenia in the CNS at different stages of illness." Brain Res. **1239:235-48.**(doi): 10.1016/j.brainres.2008.1008.1023. Epub 2008 Aug 1016.
104. Cobia, D. J., M. J. Smith, L. Wang and J. G. Csernansky (2012). "Longitudinal progression of frontal and temporal lobe changes in schizophrenia." Schizophr Res **139**(1-3): 1-6.
105. Stone, J. M., P. D. Morrison and L. S. Pilowsky (2007). "Glutamate and dopamine dysregulation in schizophrenia--a synthesis and selective review." J Psychopharmacol **21**(4): 440-452.
106. Malaspina, D. (2006). "Schizophrenia: a neurodevelopmental or a neurodegenerative disorder." J Clin Psychiatry **67**(8): e07.
107. Pantelis, C., M. Yucel, S. J. Wood, P. D. McGorry and D. Velakoulis (2003). "Early and late neurodevelopmental disturbances in schizophrenia

and their functional consequences." Aust N Z J Psychiatry **37**(4): 399-406.
108. Keshavan, M. S. (1999). "Development, disease and degeneration in schizophrenia: a unitary pathophysiological model." J Psychiatr Res **33**(6): 513-521.
109. Woods, B. T. (1998). "Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism." Am J Psychiatry **155**(12): 1661-1670.

PAPER 2

TITLE PAGE

Word count (main text): 3115
Word count (abstract): 249
tables: 1
figures: 3 composite pictures
supplemental information: 2 figures and 4 tables

Abnormal event related oscillatory responses in early psychosis

Miguel Constante[1,2*], Nicolas Crossley[1], Madiha Shaikh[1], Anirban Dutt[1], Daniel H Mathalon[3], Robin M Murray[1], Elvira Bramon[4].

[1] Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK.

[2] Hospital Beatriz Ângelo, Lisbon, Portugal.

[3] Psychiatry Service, San Francisco VA Medical Center San Francisco, CA, USA.

[4]Mental Health Sciences Unit & Institute of Cognitive Neuroscience, University College London, UK

Key words: schizophrenia; salience; event related oscillations; P300; MMN; gating.

*Corresponding author: Dr Miguel Constante, Hospital Beatriz Ângelo, Departamento de Psiquiatria e Saúde Mental, Avenida Carlos Teixeira nº3, 2674-514 Loures, Portugal.

Email address: miguel.constante@kcl.ac.uk).

ABSTRACT

Background: Brain Event-Related Oscillations (EROs) have been established as neurophysiological markers of cognitive function. Three auditory paradigms, classically used to elicit the P300 and Mismatch Negativity (MMN) components and P50 gating, share links to attention function and have shown impairments in schizophrenia. We hypothesized that early psychosis patients would show auditory EROs deficits and these would be associated to psychosis symptoms and illness duration.

Methods: Patients with early psychosis (n=35) and gender/age-matched controls (n=35) underwent electroencephalography recording during an auditory oddball task, a duration-deviant MMN paradigm, and a paired-click paradigm. Wavelet-based time-frequency analyses were conducted to assess single trial power. Relevant EROs clusters were identified by examining EROs task (condition) effects, associations between EROs and reaction time (RT) and EROs differences between groups, through cluster based t-tests and regression analysis. EROs measures from all three paradigms were compared between groups using ANOVA and regressed with psychosis symptoms and illness duration.

Results: Early psychosis patients showed reduced oddball task, passive oddball EROs, as well as paired-click paradigm EROs gating, respectively markers of selective attention, salience and sensory gating. The ratio $\frac{\text{passive oddball EROs}}{low\ frequency\ EROs\ gating}$ predicted oddball task EROs in controls, but not in patients. EROs gating increased with age in controls, but not in patients. The ratio $\frac{\text{oddball task EROs}}{low\ frequency\ EROs\ gating}$ increased with psychosis illness duration. EROs gating predicted PANSS negative symptoms.

Conclusions: In early psychosis, attention-related auditory EROs are impaired, show abnormal brain maturation and reflect psychopathology, but also indicate partial recovery in brain function.

INTRODUCTION

Event-related brain oscillations (EROs) correspond to changes in the frequency spectrum of the ongoing electroencephalogram (EEG), triggered by events such as an auditory stimulus. EROs amplitude (or power) can be measured for specific frequency bands with a millisecond time resolution. Time-frequency decomposition of single trials provides a measure of power that is not phase locked to the stimulus onset, complementing the information provided by ERPs (1).

EROs have been correlated with different aspects of cognition (2). While the study of EROs in schizophrenia has received increasing interest in recent years (3-7), neurophysiological studies in schizophrenia have mostly looked at event related potentials (ERP), particularly using auditory P300 (8), P50 gating (8-10) and mismatch negativity (MMN) (11-13), all of which affected in psychosis patients. The P300 is linked to cognitive information processing, including memory, attention and executive functions (14, 15); P50 ratio measures brain sensory gating, its ability to filter incoming irrelevant stimuli and focus attention (16); MMN measures an involuntary attention-call signal to auditory change (17). Arguably, attention and its key mechanism of salience detection (18), a core element of schizophrenia etiopathogenesis (19), modulate brain's reactions in the oddball task (20), passive oddball (21) and paired-click paradigms (22, 23). Moreover, combining different neurophysiological paradigms on the same sample of patients is potentially advantageous, because they can complement each other and characterize the population more accurately (24, 25). There have been reports of associations between MMN-P300 (26, 27) and P50 gating-MMN (26, 28) deficits in schizophrenia.

Previous studies in chronic patients with schizophrenia have found power reductions in delta and theta bands in the auditory oddball target detection paradigm that are associated with decreased P300 amplitude (29-31). In the paired-click paradigm, EEG power reductions in theta/alpha (32, 33) and beta (34) frequency bands contributed to decreased P50 or N100 gating in schizophrenia patients. Dependence of MMN amplitude on theta band oscillations has been shown in healthy subjects (35), and MMN theta-alpha range oscillations were abnormally enhanced in chronic schizophrenia patients (36). However, as these studies of EROs have

mostly been conducted in chronic patients, the status of attention-related EROs in early psychosis remains uncertain. Finding biomarkers of psychosis in this critical disease period, could prove valuable for instance in guiding diagnosis and treatment interventions after a first psychotic episode. Our study hypotheses were: 1) Selective attention, salience detection and sensory gating EROs are impaired in early psychosis patients, 2) influenced by psychosis illness duration and 3) psychosis severity, as measured by psychosis symptoms.

METHODS

Participants

35 participants between 18-35 years old meeting DSM-IV criteria for a psychotic disorder (see Table 1) with an onset of psychotic symptoms within the past 5 years were recruited from the early intervention services at the South London and Maudsley NHS Foundation Trust. Another 35 age and gender matched controls without a family history of psychosis were recruited from the same geographical area as the patients. Control volunteers were not excluded for a personal history of other non-psychotic DSM-IV diagnoses, provided the volunteer had been well and free from any psychotropic medication for at least 12 months prior to study entry. Patient and control participants were excluded if they had a history of neurological disorders, head injury with loss of consciousness longer than a couple of minutes or a DSM-IV diagnosis of alcohol or illegal substance dependence in the 12 months prior to study entry. Demographic and clinical data are summarized in Table 1. All participants gave written informed consent to enter the study. This research was approved by the Ethical Committee at the Institute of Psychiatry.

Table 1. Demographic and clinical variables

		Controls (N=35)	Patients (N=35)	*Statistical comparison* Test(df)	p value
Sex (% Male)		67	74	$\chi^2(1)=0.5$	0.47
Mean Age, years (SD)		25.0(4.4)	24.9(4.1)	t=0.1	0.88
Smoking status, % smokers		4.8	73.5	$\chi^2(1)=38.8$	**<0.001**
P300 amplitude (Pz)		11.8(6.6) µV	8.8(6.2) µV	(appendix Figure 2a)	
Reaction Time (RT)		422(110) ms	507(176) ms	t=-2.5, Δ=-90ms, 95% CI=-161 to -18ms, p=0.01	
Target response accuracy		95(6.7) %	91(9.1) %	t=-1.2, Δ=2.4%, 95% CI=-1.5 to 6.3 %, p=0.22	
MMN amplitude (Fz)		-4.0(3.6) µV	-2.9(3.3) µV	(appendix Figure 2b)	
P50 gating (Cz) S2/S1		0.52(0.35)	0.81(0.69)	t=-2.09, Δ=-0.29, 95% CI=-0.56 to -0.01, p=0.04	
Patients DSM-IV Diagnosis		Paranoid Schizophrenia (22) Bipolar I disorder (5) Schizophreniform disorder (3) Acute and transient Psychotic disorder (3) Schizoaffective disorder (1) Major Depressive Disorder with Psychotic features (1)			
Patients duration of illness in months - mean (SD)		23.2 (15.4)			
Psychotropic Medication (number of patients)		Risperidone (11) Olanzapine (10) Aripiprazole (5) Sodium Valproate (5) Citalopram (3)	Amisulpride (1) Quetiapine (1) Haloperidol (1) Sertraline (1) No medication (6)		
PANSS	**PS**	10.3 (3.9)			
	NS	18.2 (8.3)			
	GS	29.3 (8.2)			
	TS	57.8 (17.8)			

Values for categorical variables are shown as frequency (N) and for continuous variables as Mean (Standard Deviation). Comparisons were performed using t-test for continuous and chi-square for categorical variables; 95% confidence intervals (CI) are presented; df – degrees of freedom; SD - standard deviation. PANSS, Positive and Negative Syndrome Scale; PS, positive symptoms; NS, negative symptoms; GS, General symptoms; TS, total symptoms.

EEG recording

EEG data was recorded using a 40-channel Quik-Cap electrode cap positioned according to the 10/20 International System referenced to linked mastoids and grounded at Fpz, a SCAN NuAmps Express™ 40-channel monopolar digital amplifier and SCAN software package version 4.3 (Compumedics Neuroscan, Texas, USA). Eye movements were recorded from the

outer canthus of each eye and above and below the right eye. Electrode impedances were below 5 kΩ. Data were continuously digitised at 1000 Hz with a digital 0.1-100 Hz band pass filter (24 dB/octave roll-off). **S**ubjects were asked not to smoke for at least 30 minutes before data collection (37). Data analysis was performed offline using the Matlab-based FieldTrip toolbox (http://fieldtrip.fcdonders.nl/). Continuous EEG data were segmented into large epochs time-locked to auditory stimuli (–3100 to 2500 ms), in order to allow analysis of low frequency bands and minimize edge effects. Artefact rejection was performed to reject data segments containing eye blinks, muscle artefacts and amplitudes exceeding +/- 100 μV. Line noise removal was performed at 50Hz using a discrete Fourier transform.

Participants performed an auditory oddball task (38, 39) using one block of four hundred 80 dB tones presented through bilateral earphones, with a 2 second (±0.2 second) inter-stimulus interval. The tones comprised a random sequence of 80% 'standards' (1000 Hz) and 20% 'targets' (1500 Hz). Subjects were instructed to press a button with their preferred hand in response to target tones only. Trials with correctly identified target tones were used for analysis. To yield the target ERP waveforms the EEG was digitally filtered (0.05–40 Hz) and baseline corrected (–50 to 0 ms), then epochs were averaged. P300 peak amplitude was measured at Pz, calculating the peak (between 250 to 400ms) to preceding trough difference.

A passive oddball (duration-deviant MMN paradigm) was carried out (13) whilst subjects were instructed to remain still and quiet, keep their eyes open focusing on a written sign, and disregard the sounds presented to them. We used three blocks of 400 binaural 80-dB stimuli (0.3 sec inter-stimulus interval) comprising 85% standards (25 ms, 1000 Hz, 5-ms rise/fall time) and 15% duration deviants (50 ms, 1000 Hz, 5 ms rise/fall time). MMN was extracted by subtracting the averaged waveforms for the standard stimuli from those for the deviant stimuli, after filtering (0.03–40 Hz) and baseline correction (–50 to 0 ms). Peak amplitude of the mismatch negativity waveform was measured at Fz, calculating the difference between mean MMN (130 to 190ms) and MMN baseline (-50 to 0ms).

Participants also underwent a paired-click paradigm (40, 41). S1 and S2 clicks were of 1 ms duration and separated by 500 ms. Intertrial intervals between click pairs were 10 seconds.

Subjects were presented with four or five blocks of 30 pairs of conditioning and test clicks and instructed to avoid blinking during the click presentations. Stimulus intensity was adjusted individually to 43 dB above the hearing threshold. To obtain the ERP, the EEG signal was filtered (10Hz high-pass filter), corrected for baseline values (–50 to 0 ms) and epochs were averaged separately for the first click (S1) and the second click (S2). . P50 peak amplitudes for S1 and S2 were measured at the Cz site, in the 50–70ms post-stimulus interval, using a computer algorithm. S2 P50 latency had to be a value within ± 10 ms of S1 P50 latency and P50 amplitude was measured relative to its preceding through. S1 P50 waves with less than 0.5 μV were excluded. P50 ratio was calculated as S2/S1 P50.

The three experiments were carried out in the above order, their duration was approximately 15, 6 and 20-25 minutes, respectively.

Time-frequency analyses

Time-frequency analyses were performed using the same artifact-free data segments used in the ERP processing pipeline, before filtering or averaging. Power was extracted from single trials using the 'wavelet method' based on Morlet wavelets with a 'width' of 4 (6), 1Hz (frequency) and 1msec (time) resolution. The EEG frequency bands of interest were Delta (1-3Hz), Theta (4-7Hz), Alpha (8-12Hz), Beta (13-30Hz) and Gamma (31-100Hz). For EROs calculation, relative baseline correction (the quotient of post stimuli power over baseline average power) was applied and baseline lengths were determined separately for each band: Delta (-1000 to 0 ms), Theta (-250 to 0 ms), Alpha (-125 to 0 ms), Beta (-100 to 0 ms), Gamma (-50 to 0 ms). EROs represent the relative change of spectral power in comparison to the baseline.

Statistical Analysis

Group differences for mean RT, target response accuracy and P50 S2/S1 amplitude ratios were tested by univariate t-test. EROs differences between groups and conditions (tow tone types) were analyzed using independent and dependent samples t-tests respectively and the associations between EROs and psychosis symptoms/oddball task reaction time (RT), were

analyzed using linear regression. These results were adjusted for multiple comparisons by means of a cluster based test statistic (for temporal and spectral adjacency) with a threshold alpha=0.05; Monte Carlo significance probability was calculated using 1000 random partitions, the maximum of the cluster-level summed t-values and a cluster threshold alpha=0.05 (42). EROs were measured from each of the tested paradigms, within the time-frequency boundaries of the clusters showing overlap between condition, oddball task reaction time (RT) and/or group effects (Figures 1 and 2), thus selecting EROs of interest. Because in the passive oddball paradigm there was no group effect on isolated EROs clusters, we included all deviant tone EROs clusters that were associated with the condition effect, given this functional link between them. This was applied equally to all subjects as follows: *Oddball task EROs* - target tone maximum EROs value, measured within the time-frequency boundaries of the delta-theta cluster associated with the group effect (Figure 2a). *Passive oddball EROs* - the ratio between mean deviant tone EROs within the condition effect associated gamma and theta positive clusters, and the minimum EROs value within the beta negative cluster boundaries (Figure 1b). *Paired-click low frequency EROs gating* - the minimum S2/S1 EROs ratio value, measured within the group effect associated delta-theta cluster boundaries (Figure 2d). EROs extracted from each paradigm were compared between groups using ANOVA, including a fixed factor for gender and age as covariate. Correlations between each paradigm EROs were performed, with bonferroni correction. An ANOVA model with an interaction term clinical group * $\frac{\text{passive oddball EROs}}{\text{paired-click paradigm EROs gating}}$, as independent variable and oddball task EROs as dependent variable, was used to test the relationship between sensory driven and top down EROs in the two study groups. EROs were entered in regression analysis as independent variables, to predict age, illness duration, PANSS positive and negative symptoms subscales. EROs were transformed into zscores and combined as: oddball task + passive oddball - low frequency EROs gating, to perform ROC curve analysis.

RESULTS

Event-related potentials and behavioral results

The grand average ERP waveforms for patient and control groups of the P300 at Pz, MMN at Fz and P50/N100 at Cz, are displayed in Figures 1d, 1e and 1f respectively, with their characteristic form widely described in the literature. As expected from previous studies, controls showed significantly larger P300 and MMN amplitudes, smaller P50 ratio (Appendix Figures 2a and 2b) and faster RTs, there no group difference in target response accuracy (Table 1).

Time-frequency analysis by test condition

The condition effects (two tone types comparisons) for the 3 studied paradigms in the overall sample (patients and controls combined) are shown in Figures 1a-c t-test scores. Oddball task target tones elicited larger delta/theta frequency range and late gamma EROs, but smaller alpha EROs than standard tones (Figure 1a). Passive oddball deviant tones elicited larger early gamma and delta/theta EROs, but smaller late beta EROs than standard tones (Figure 1b). From the paired-click paradigm, S1 elicited larger delta/theta EROs but smaller gamma EROs than S2 (Figure 1c).

Figure 1

EROs condition effects across all subjects

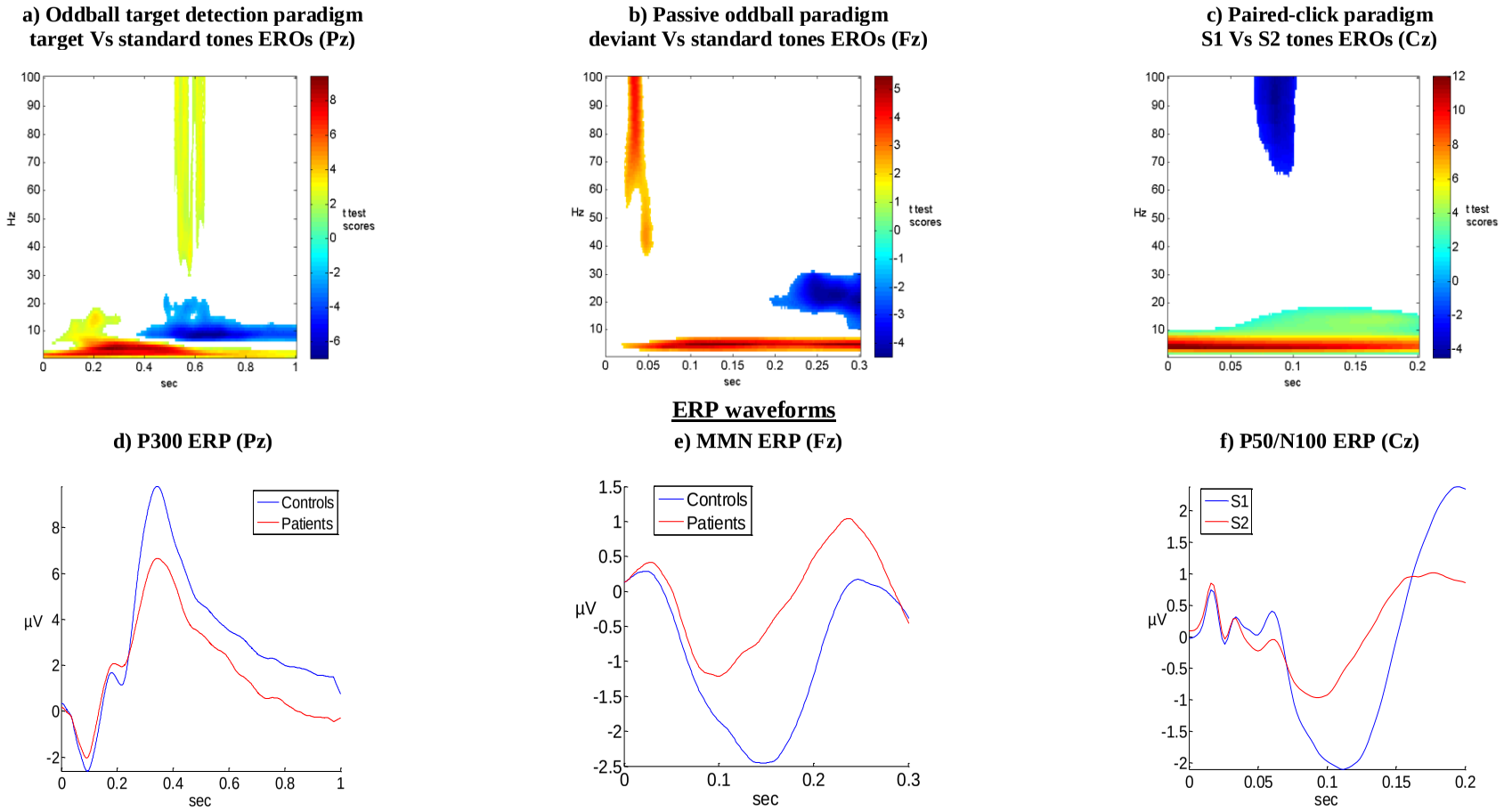


Figure 1. a) t-test scores for comparisons between target Vs standard tones EROs time-frequency spectrums from the oddball target detection paradigm at Pz electrode. b) t-test scores for comparisons between deviant Vs standard tones EROs time-frequency spectrums from the passive oddball (MMN) paradigm at Fz electrode. c) t-test scores for comparisons between S1 Vs S2 tones EROs time-frequency spectrums, from the paired-click paradigm, at Cz electrode. EEG frequency is indicated on the y-axis and time is indicated on the x-axis. T-test scores are indicated on a colour scale located to the far right of each plot. All subjects were included in analyses (controls and patients combined). All results are adjusted for multiple comparisons and a mask (white coulour) applied for non significant comparisons, using a significance threshold of $p<.05$. d) and e) P300 and MMN grand average waveforms for controls and patients. f) P50/N100 grand average waveforms for all subjects combined. Amplitude (microV) is plotted over time (seconds). Time zero denotes the occurrence of stimuli.

EROs clinical group comparisons and associations with oddball task reaction time

Oddball task

T-test scores in Figure 2a show reduced target tone delta/theta EROs in patients compared to controls. A similar difference was found for the oddball task non-target tone (not shown). Linear regression coefficients in Figure 2b show three time-frequency EROs clusters, associating target tone EROs with RT in all subjects. As such, smaller task-related EROs in early and late gamma and low frequencies were markers of slower RT. Conversely, mid-latency gamma and late alpha/beta EROs were positively associated with RT.

Passive oddball paradigm

No between groups differences were found for deviant or standard tones EROs time-frequency spectrums. Linear regression coefficients in Figure 2c show a positive association between patients' deviant-standard tone late beta frequency range EROs difference and oddball task RT; thus, as deviant tone late beta EROs increase relative to the standard tone, RT is slower.

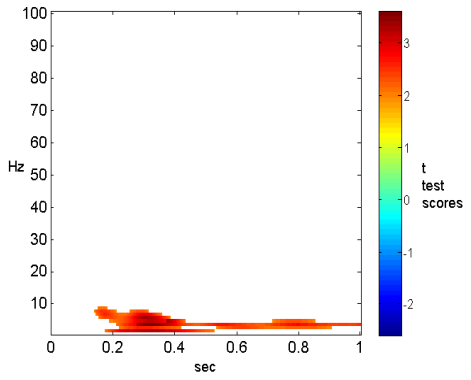
Paired-click paradigm

No between-group differences were found for S1 or S2 tone EROs time-frequency spectrums. T-test scores in Figure 2d show smaller S2/S1 theta EROs ratios in controls compared to patients. Linear regression coefficients in Figure 2e show a positive association between patients' S2/S1 theta EROs ratio and oddball task RT; thus, worse low frequency EROs gating is linked to slower RT.

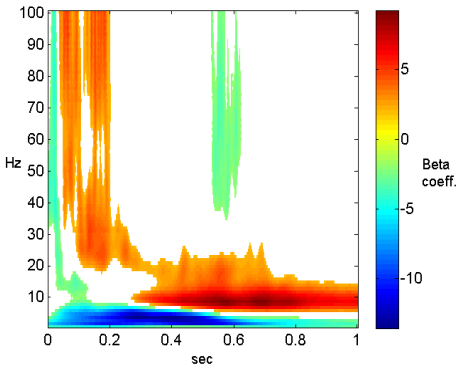
Figure 2

Oddball task paradigm

a) Target tone EROs - controls Vs patients (Pz)

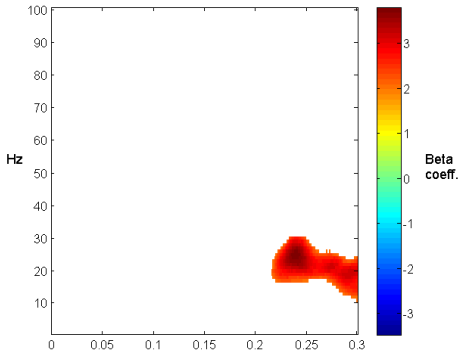


b) Target tone EROs and reaction time (Pz)



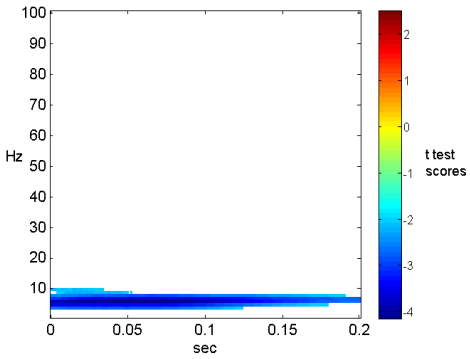
Passive oddball paradigm

c) Deviant-Standard tone EROs and reaction time (Fz)



Paired-click paradigm

d) S2/S1 EROs ratio - controls Vs patients (Cz)



e) S2/S1 EROs ratio and oddball task reaction time (Cz)

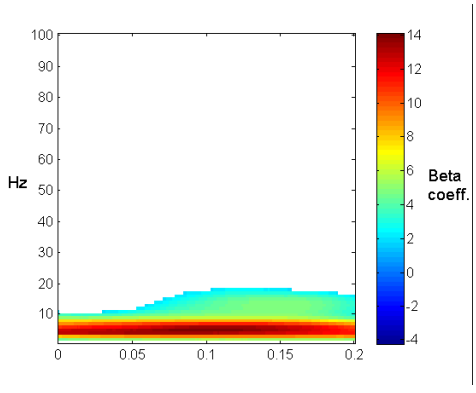


Figure 2. **a)** T-test scores (colour scale located to the far right of the plot) for comparisons between controls Vs patients target tone EROs time-frequency spectrums from the oddball task, at Pz electrode. **b)** Linear regression coefficients for the association between target tone EROs time-frequency spectrum and reaction time (RT). **c)** Linear regression coefficients for the association between passive oddball (MMN) paradigm EROs difference (deviant-stantard) and RT, at Fz electrode. **d)** T-test scores for comparisons between controls Vs patients S2/S1 EROs time-frequency spectrum at Cz electrode. **e)** Linear regression coefficients for the association between S2/S1 EROs time-frequency spectrum and RT. EEG frequency is indicated on the y-axis and time is indicated on the x-axis; results are adjusted for multiple comparisons and then a mask (white colour) applied for non significant comparisons, using a significance threshold of $p<.05$. Associations between EROs and RT included all study subjects (controls and patients combined).

EROs groups comparisons, relationships between EROs and their associations with clinical variables

EROs extracted from each of the tested paradigms were compared between groups using ANOVA. Patients showed deficits in the three paradigms, with significant estimated marginal means group effects on oddball task EROs, $F(1,68)=13.99$, $p<0.001$, passive oddball EROs, $F(1,68)=7.20$, $p=0.009$ and low frequency EROs gating, $F(1,68)=11.18$, $p=0.001$. Group *x* age interaction effects showed that with increasing age, low frequency EROs gating values decreased in the controls group, but not in the patients group (appendix Tables 1-3 and Figure 3b). Oddball task EROs and low frequency EROs gating were correlated in the patients group ($r = -0.45$, $p=0.05$), there were no other significant correlations between EROs in patients or controls groups. The ratio $\frac{\text{passive oddball EROs}}{\text{low frequency EROs gating}}$ predicted oddball task EROs in controls, $F(1,68)=6.11$, $p=0.004$ ($\beta=0.55$, $t=2.82$, $p=0.006$), but not in patients ($\beta=0.21$, $t=0.82$, $p=0.41$). Results of regression analysis looking at associations between extracted EROs and clinical variables are displayed in appendix Table 4. The ratio $\frac{\text{oddball task EROs}}{\text{low frequency EROs gating}}$ increased with duration of psychosis illness (see also Figure 3c). Low frequency and high frequency EROs gating were independently positively associated with PANSS negative symptoms (see also Figure 3d). No association was found between EROs and PANSS positive symptoms.

ROC curve using the three paradigms combined EROs as independent variable, is shown in Figure 3a. The area under the curve is 0.82, with SE=0.05 and 95% CI 0.72 to 0.92, at the optimum ROC point: sensitivity = 0.65 and specificity = 0.94.

Figure 3

a) Combined EROs descriminatory ability

b) Age related changes in EROs - controls Vs patients

c) EROs and psychosis illness duration

d) EROs and PANSS negative symptoms

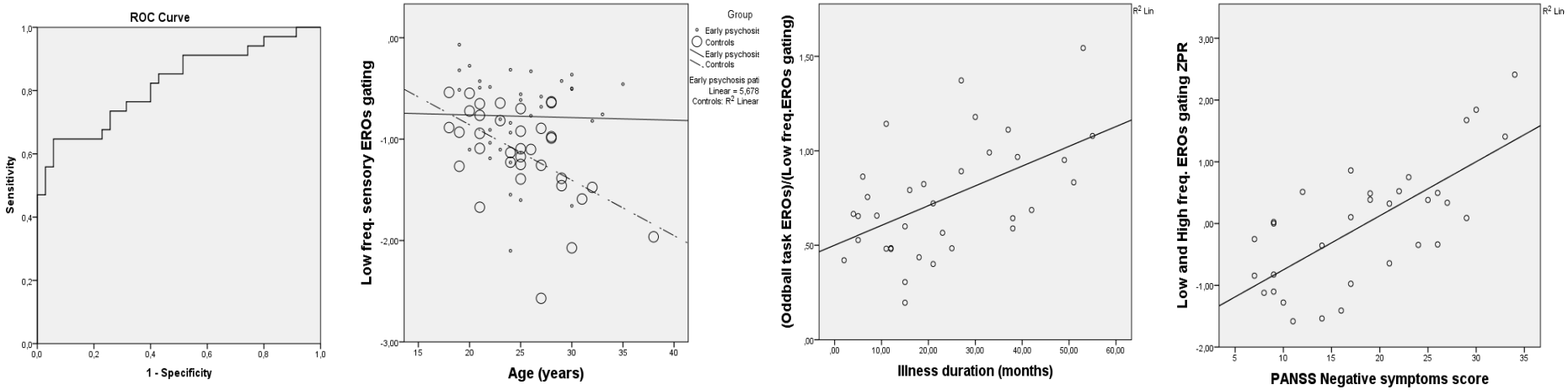


Figure 3. a) ROC curve for oddball task, passive oddball and paired-click paradigms EROs combined descriminatory ability between controls and patients. **b)** and **c)** scatter plots and fitted regression lines showing the relationship between paired-click paradigm low frequency EROs gating as independent variable and age or illness duration as dependent variables, respectively; **b)** with advancing age, within the studied 18-35 age interval, controls show increasing sensory gating, which does not occur in patients; **c)** with increasing duration of illness, early psychosis patients show an increasing ratio between selective attention resource allocation and sensory gating; **d)** scatter plot with fitted regression line showing the relationship between low and high frequency EROs gating and PANSS negative symptoms score; worse EROs gating is associated with worse symptoms. ZPR - regression standardized predicted values.

DISCUSSION

Our results provide insights into normal brain neurophysiology and how it is impacted upon by psychosis. The studied EROs display a physiological pattern, marking conscious attention and stimulus salience attribution in the auditory oddball task and passive oddball paradigms (43). This pattern consists of increased EROs, first in the early gamma and then in low frequencies (delta/theta), a "fast-to-slow" transition (44) that has been attributed to a change from early sensory perception to encoding functions (45, 46), followed by attenuated EROs at higher frequencies (alpha to gamma). The EROs increase possibly reflects underlying excitatory brain activity and allocation of brain resources to stimulus processing (47). Cortical excitatory pyramidal neurons may then be physiologically kept in check by feedback inhibition, mediated by high frequency inhibitory interneurons that set firing rates back into a functional range (48, 49).The attenuation of these inhibitory EROs could indicate a state of increased arousal or brain excitability (50, 51). Alpha event-related desynchronization, in particular, is thought to reflect attentional demands and cortex release from inhibition (52), it has previously been found associated to stimulus relevance evaluation in the oddball task (53) and impaired in schizophrenia patients (54). Within these dynamics, the functional roles of early gamma EROs, related to sensory processing and late gamma EROs, related to cognition (55, 56), are tapped on by the passive oddball and oddball task paradigms deviant and target tone effects, respectively. There is evidence, from studies where psychosis mimicking substances ketamine and dexamphetamine (57-59) were administered to healthy subjects, for an inverse association between higher and lower frequencies EROs. It has been proposed that, in schizophrenia, inhibitory inputs from GABAergic interneurons to pyramidal neurons, through gamma oscillations, are reduced as a downstream homeostatic response to maintain excitatory/inhibitory balance, in the face of impaired excitatory activity (60). Stahl (61) conceptualized a neurochemical schizophrenia model where dysfunctional glutamate-activated GABA interneurons are linked to abnormal dopaminergic activity, producing psychosis symptoms.

We found early psychosis patients showed deficits in each of the studied paradigms and also disrupted connection between sensory driven (passive oddball and paired-click paradigms) and top down (oddball task) EROs. Sensory gating increase with age may be a maturational change (62), that we observed in the controls group, but not in the early psychosis patients sample. Healthy subjects brains develop increasing efficiency, during early adulthood, resulting in lesser need to recruit cognitive capacity (63), whereas psychosis patients have been shown to have abnormal maturation of attentional performance (64). On the other hand, oddball task and low frequency EROs gating increased with advancing duration of psychotic illness (Figure 3c). This supports the possibility of a partial recovery in brain function (65, 66), following a "hit" around disease onset (67). Poorer low and high frequency EROs gating was associated with worse psychopathology in early psychosis patients, suggesting these symptoms bear relationship with the specific impairment of brain gating mechanisms and the extent to their improvement following disease onset. Our results indicate the coexistence of several processes influencing brain function during early psychosis: acquired deficits, disrupted maturation, but also partial recovery; this complexity fits with the controversies around the longitudinal course of brain function in psychosis (68). Previous ERP and neuropsychological studies showed a mixed picture, where some neurophysiological deficits progress, with increasing risk of transition to psychosis, whereas others do not (69-83).

Our study has limitations: we could not perform subgroup analysis, looking at diagnostic specificity (84-88), due to the small numbers. Only one electrode per paradigm was analyzed, topographical effects and brain sources were not investigated; this approach, however, reduced multiple comparisons and makes data collection/analysis easier, thus facilitating potential translation to clinical application. We did not control for medication (5, 89) as the drugs prescribed were too heterogeneous, or smoking (37) effects.

In conclusion, in early psychosis, attention function related neurophysiological markers show impairment, reveal disrupted brain maturation and reflect psychosis symptoms severity, but also indicate partial recovery in brain function.

ACKNOWLEDGEMENTS

N Crossley is funded by a Wellcome Trust Fellowship. E. Bramon currently holds a Medical Research Council (MRC) New Investigator Award and a MRC Centenary Award. Further support to EB was provided by the National Institute of Health Research UK (post-doctoral fellowship), the Brain and Behavior Research foundation's (two NARSAD's Young Investigator Awards) and a Wellcome Trust Research Training Fellowship. This project was also funded by the Psychiatry Research Trust and the Schizophrenia Research Fund. A. Dutt was partly supported by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry at King's College London.

REFERENCES

1. Makeig, S., S. Debener, J. Onton and A. Delorme (2004). "Mining event-related brain dynamics." Trends Cogn Sci **8**(5): 204-210.
2. Basar, E., C. Basar-Eroglu, S. Karakas and M. Schurmann (2001). "Gamma, alpha, delta, and theta oscillations govern cognitive processes." Int J Psychophysiol **39**(2-3): 241-248.
3. Moran, L. V. and L. E. Hong (2011). "High vs low frequency neural oscillations in schizophrenia." Schizophr Bull **37**(4): 659-663.
4. Uhlhaas, P. J. and W. Singer (2010). "Abnormal neural oscillations and synchrony in schizophrenia." Nat Rev Neurosci **11**(2): 100-113.
5. Basar, E. and B. Guntekin (2008). "A review of brain oscillations in cognitive disorders and the role of neurotransmitters." Brain Res **1235**: 172-193.
6. Roach, B. J. and D. H. Mathalon (2008). "Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia." Schizophr Bull **34**(5): 907-926.
7. van der Stelt, O. and A. Belger (2007). "Application of electroencephalography to the study of cognitive and brain functions in schizophrenia." Schizophr Bull **33**(4): 955-970.
8. Bramon, E., S. Rabe-Hesketh, P. Sham, R. M. Murray and S. Frangou (2004). "Meta-analysis of the P300 and P50 waveforms in schizophrenia." Schizophr Res **70**(2-3): 315-329.
9. Olincy, A., D. L. Braff, L. E. Adler, K. S. Cadenhead, M. E. Calkins, D. J. Dobie, M. F. Green, T. A. Greenwood, R. E. Gur, R. C. Gur, G. A. Light, J. Mintz, K. H. Nuechterlein, A. D. Radant, N. J. Schork, L. J. Seidman, L. J. Siever, J. M. Silverman, W. S. Stone, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang, B. I. Turetsky, B. D. Wagner and R. Freedman (2010). "Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the Consortium on Genetics of Schizophrenia." Schizophr Res **119**(1-3): 175-182.
10. Patterson, J. V., W. P. Hetrick, N. N. Boutros, Y. Jin, C. Sandman, H. Stern, S. Potkin and W. E. Bunney, Jr. (2008). "P50 sensory gating ratios in schizophrenics and controls: a review and data analysis." Psychiatry Res **158**(2): 226-247.
11. Naatanen, R. and S. Kahkonen (2009). "Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review." Int J Neuropsychopharmacol **12**(1): 125-135.
12. Umbricht, D. and S. Krljes (2005). "Mismatch negativity in schizophrenia: a meta-analysis." Schizophr Res **76**(1): 1-23.
13. Bramon, E., R. J. Croft, C. McDonald, G. K. Virdi, J. G. Gruzelier, T. Baldeweg, P. C. Sham, S. Frangou and R. M. Murray (2004). "Mismatch negativity in schizophrenia: a family study." Schizophr Res **67**(1): 1-10.
14. Polich, J. (2007). "Updating P300: an integrative theory of P3a and P3b." Clin Neurophysiol **118**(10): 2128-2148.
15. Sutton, S., M. Braren, J. Zubin and E. R. John (1965). "Evoked-potential correlates of stimulus uncertainty." Science **150**(3700): 1187-1188.
16. Freedman, R., M. Waldo, P. Bickford-Wimer and H. Nagamoto (1991). "Elementary neuronal dysfunctions in schizophrenia." Schizophr Res **4**(2): 233-243.
17. Naatanen, R., T. Kujala and I. Winkler (2011). "Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses." Psychophysiology **48**(1): 4-22.
18. Corbetta, M. and G. L. Shulman (2002). "Control of goal-directed and stimulus-driven attention in the brain." Nat Rev Neurosci **3**(3): 201-215.
19. Kapur, S. (2003). "Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia." Am J Psychiatry **160**(1): 13-23.
20. Coull, J. T. (1998). "Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology." Prog Neurobiol **55**(4): 343-361.
21. Todd, J., P. T. Michie, U. Schall, P. B. Ward and S. V. Catts (2012). "Mismatch negativity (MMN) reduction in schizophrenia-impaired prediction--error generation, estimation or salience?" Int J Psychophysiol **83**(2): 222-231.
22. Rosburg, T., P. Trautner, C. E. Elger and M. Kurthen (2009). "Attention effects on sensory gating--intracranial and scalp recordings." Neuroimage **48**(3): 554-563.
23. Potter, D., A. Summerfelt, J. Gold and R. W. Buchanan (2006). "Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia." Schizophr Bull **32**(4): 692-700.
24. Turetsky, B. I., W. B. Bilker, S. J. Siegel, C. G. Kohler and R. E. Gur (2009). "Profile of auditory information-processing deficits in schizophrenia." Psychiatry Res **165**(1-2): 27-37.
25. Price, G. W., P. T. Michie, J. Johnston, H. Innes-Brown, A. Kent, P. Clissa and A. V. Jablensky (2006). "A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia." Biol Psychiatry **60**(1): 1-10.
26. Gjini, K., C. Arfken and N. N. Boutros (2010). "Relationships between sensory "gating out" and sensory "gating in" of auditory evoked potentials in schizophrenia: a pilot study." Schizophr Res **121**(1-3): 139-145.
27. Leitman, D. I., P. Sehatpour, B. A. Higgins, J. J. Foxe, G. Silipo and D. C. Javitt (2010). "Sensory deficits and distributed hierarchical dysfunction in schizophrenia." Am J Psychiatry **167**(7): 818-827.
28. Kisley, M. A., T. L. Noecker and P. M. Guinther (2004). "Comparison of sensory gating to mismatch negativity and self-reported perceptual

phenomena in healthy adults." Psychophysiology **41**(4): 604-612.
29. Doege, K., A. T. Bates, T. P. White, D. Das, M. P. Boks and P. F. Liddle (2009). "Reduced event-related low frequency EEG activity in schizophrenia during an auditory oddball task." Psychophysiology **46**(3): 566-577.
30. Ford, J. M., B. J. Roach, R. S. Hoffman and D. H. Mathalon (2008). "The dependence of P300 amplitude on gamma synchrony breaks down in schizophrenia." Brain Res **1235**: 133-142.
31. Roschke, J. and J. Fell (1997). "Spectral analysis of P300 generation in depression and schizophrenia." Neuropsychobiology **35**(2): 108-114.
32. Brockhaus-Dumke, A., R. Mueller, U. Faigle and J. Klosterkoetter (2008). "Sensory gating revisited: relation between brain oscillations and auditory evoked potentials in schizophrenia." Schizophr Res **99**(1-3): 238-249.
33. Jansen, B. H., A. Hegde and N. N. Boutros (2004). "Contribution of different EEG frequencies to auditory evoked potential abnormalities in schizophrenia." Clin Neurophysiol **115**(3): 523-533.
34. Hong, L. E., A. Summerfelt, R. P. McMahon, G. K. Thaker and R. W. Buchanan (2004). "Gamma/beta oscillation and sensory gating deficit in schizophrenia." Neuroreport **15**(1): 155-159.
35. Fuentemilla, L., J. Marco-Pallares, T. F. Munte and C. Grau (2008). "Theta EEG oscillatory activity and auditory change detection." Brain Res **1220**: 93-101.
36. Elliot Hong, L., L. V. Moran, X. Du, P. O'Donnell and A. Summerfelt (2012). "Mismatch negativity and low frequency oscillations in schizophrenia families." Clin Neurophysiol **123**(10): 1980-1988.
37. Adler, L. E., L. D. Hoffer, A. Wiser and R. Freedman (1993). "Normalization of auditory physiology by cigarette smoking in schizophrenic patients." Am J Psychiatry **150**(12): 1856-1861.
38. Bramon, E., C. McDonald, R. J. Croft, S. Landau, F. Filbey, J. H. Gruzelier, P. C. Sham, S. Frangou and R. M. Murray (2005). "Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study." Neuroimage **27**(4): 960-968.
39. Schulze, K. K., M. H. Hall, C. McDonald, N. Marshall, M. Walshe, R. M. Murray and E. Bramon (2008). "Auditory P300 in patients with bipolar disorder and their unaffected relatives." Bipolar Disord **10**(3): 377-386.
40. Schulze, K. K., M. H. Hall, C. McDonald, N. Marshall, M. Walshe, R. M. Murray and E. Bramon (2007). "P50 auditory evoked potential suppression in bipolar disorder patients with psychotic features and their unaffected relatives." Biol Psychiatry **62**(2): 121-128.
41. Hall, M. H., K. Schulze, P. Sham, S. Kalidindi, C. McDonald, E. Bramon, D. L. Levy, R. M. Murray and F. Rijsdijk (2008). "Further evidence for shared genetic effects between psychotic bipolar disorder and P50 suppression: a combined twin and family study." Am J Med Genet B Neuropsychiatr Genet **147B**(5): 619-627.
42. Maris, E. and R. Oostenveld (2007). "Nonparametric statistical testing of EEG- and MEG-data." J Neurosci Methods **164**(1): 177-190.
43. Mazaheri, A. and T. W. Picton (2005). "EEG spectral dynamics during discrimination of auditory and visual targets." Brain Res Cogn Brain Res **24**(1): 81-96.
44. Bernat, E. M., S. M. Malone, W. J. Williams, C. J. Patrick and W. G. Iacono (2007). "Decomposing delta, theta, and alpha time-frequency ERP activity from a visual oddball task using PCA." Int J Psychophysiol **64**(1): 62-74.
45. Traub, R. D., M. A. Whittington, E. H. Buhl, J. G. Jefferys and H. J. Faulkner (1999). "On the mechanism of the gamma --> beta frequency shift in neuronal oscillations induced in rat hippocampal slices by tetanic stimulation." J Neurosci **19**(3): 1088-1105.
46. Haenschel, C., T. Baldeweg, R. J. Croft, M. Whittington and J. Gruzelier (2000). "Gamma and beta frequency oscillations in response to novel auditory stimuli: A comparison of human electroencephalogram (EEG) data with in vitro models." Proc Natl Acad Sci U S A **97**(13): 7645-7650.
47. Yordanova, J., M. Devrim, V. Kolev, A. Ademoglu and T. Demiralp (2000). "Multiple time-frequency components account for the complex functional reactivity of P300." Neuroreport **11**(5): 1097-1103.
48. Knyazev, G. G. (2007). "Motivation, emotion, and their inhibitory control mirrored in brain oscillations." Neurosci Biobehav Rev **31**(3): 377-395.
49. Turrigiano, G. G. and S. B. Nelson (2004). "Homeostatic plasticity in the developing nervous system." Nat Rev Neurosci **5**(2): 97-107.
50. Neuper, C. and G. Pfurtscheller (2001). "Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates." Int J Psychophysiol **43**(1): 41-58.
51. Pfurtscheller, G. and F. H. Lopes da Silva (1999). "Event-related EEG/MEG synchronization and desynchronization: basic principles." Clin Neurophysiol **110**(11): 1842-1857.
52. Klimesch, W. (2012). "alpha-band oscillations, attention, and controlled access to stored information." Trends Cogn Sci **16**(12): 606-617.
53. Yordanova, J., V. Kolev and J. Polich (2001). "P300 and alpha event-related desynchronization (ERD)." Psychophysiology **38**(1): 143-152.
54. Higashima, M., T. Tsukada, T. Nagasawa, T. Oka, T. Okamoto, Y. Okamoto and Y. Koshino (2007). "Reduction in event-related alpha attenuation during performance of an auditory oddball task in schizophrenia." Int J Psychophysiol **65**(2): 95-102.
55. Herrmann, C. S., I. Frund and D. Lenz (2010). "Human gamma-band activity: a review on cognitive and behavioral correlates and network models." Neurosci Biobehav Rev **34**(7): 981-992.
56. Karakas, S. and E. Basar (1998). "Early gamma response is sensory in origin: a conclusion based on cross-comparison of results from multiple experimental paradigms." Int J Psychophysiol **31**(1): 13-31.
57. Hong, L. E., A. Summerfelt, R. W. Buchanan, P. O'Donnell, G. K. Thaker, M. A. Weiler and A. C. Lahti (2010). "Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine." Neuropsychopharmacology **35**(3): 632-640.
58. Albrecht, M. A., G. Price, J. Lee, R. Iyyalol and M. T. Martin-Iverson (2012). "Dexamphetamine

reduces auditory P3 delta power and phase-locking while increasing gamma power." Eur Neuropsychopharmacol **22**(10): 734-746.
59. Ehrlichman, R. S., M. J. Gandal, C. R. Maxwell, M. T. Lazarewicz, L. H. Finkel, D. Contreras, B. I. Turetsky and S. J. Siegel (2009). "N-methyl-d-aspartic acid receptor antagonist-induced frequency oscillations in mice recreate pattern of electrophysiological deficits in schizophrenia." Neuroscience **158**(2): 705-712.
60. Lewis, D. A., A. A. Curley, J. R. Glausier and D. W. Volk (2012). "Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia." Trends Neurosci **35**(1): 57-67.
61. Schwartz, T. L., S. Sachdeva and S. M. Stahl (2012). "Glutamate neurocircuitry: theoretical underpinnings in schizophrenia." Front Pharmacol **3**: 195.
62. Davies, P. L., W. P. Chang and W. J. Gavin (2009). "Maturation of sensory gating performance in children with and without sensory processing disorders." Int J Psychophysiol **72**(2): 187-197.
63. van Dinteren, R., M. Arns, M. L. Jongsma and R. P. Kessels (2014). "P300 development across the lifespan: a systematic review and meta-analysis." PLoS One **9**(2): e87347.
64. Mirzakhanian, H., F. Singh, K. Seeber, K. M. Shafer and K. S. Cadenhead (2013). "A developmental look at the attentional system in the at risk and first episode of psychosis: age related changes in attention along the psychosis spectrum." Cogn Neuropsychiatry **18**(1-2): 26-43.
65. Bozikas, V. P. and C. Andreou (2011). "Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature." Aust N Z J Psychiatry **45**(2): 93-108.
66. Jahshan, C., R. K. Heaton, S. Golshan and K. S. Cadenhead (2010). "Course of neurocognitive deficits in the prodrome and first episode of schizophrenia." Neuropsychology **24**(1): 109-120.
67. Keshavan, M. S. (1999). "Development, disease and degeneration in schizophrenia: a unitary pathophysiological model." J Psychiatr Res **33**(6): 513-521.
68. Zipursky, R. B., T. J. Reilly and R. M. Murray (2013). "The myth of schizophrenia as a progressive brain disease." Schizophr Bull **39**(6): 1363-1372.
69. Hsieh, M. H., J. C. Shan, W. L. Huang, W. C. Cheng, M. J. Chiu, F. S. Jaw, H. G. Hwu and C. C. Liu (2012). "Auditory event-related potential of subjects with suspected pre-psychotic state and first-episode psychosis." Schizophr Res **140**(1-3): 243-249.
70. Jahshan, C., K. S. Cadenhead, A. J. Rissling, K. Kirihara, D. L. Braff and G. A. Light (2012). "Automatic sensory information processing abnormalities across the illness course of schizophrenia." Psychol Med **42**(1): 85-97.
71. van Tricht, M. J., D. H. Nieman, J. T. Koelman, A. J. Mensink, L. J. Bour, J. N. van der Meer, T. A. van Amelsvoort, D. H. Linszen and L. de Haan (2012). "Sensory gating in subjects at ultra high risk for developing a psychosis before and after a first psychotic episode." World J Biol Psychiatry.
72. Brockhaus-Dumke, A., F. Schultze-Lutter, R. Mueller, I. Tendolkar, A. Bechdolf, R. Pukrop, J. Klosterkoetter and S. Ruhrmann (2008). "Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients." Biol Psychiatry **64**(5): 376-384.
73. Magno, E., S. Yeap, J. H. Thakore, H. Garavan, P. De Sanctis and J. J. Foxe (2008). "Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia." Biol Psychiatry **64**(5): 385-391.
74. Salisbury, D. F., N. Kuroki, K. Kasai, M. E. Shenton and R. W. McCarley (2007). "Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia." Arch Gen Psychiatry **64**(5): 521-529.
75. Umbricht, D. S., J. A. Bates, J. A. Lieberman, J. M. Kane and D. C. Javitt (2006). "Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia." Biol Psychiatry **59**(8): 762-772.
76. van der Stelt, O., J. A. Lieberman and A. Belger (2005). "Auditory P300 in high-risk, recent-onset and chronic schizophrenia." Schizophr Res **77**(2-3): 309-320.
77. Brockhaus-Dumke, A., I. Tendolkar, R. Pukrop, F. Schultze-Lutter, J. Klosterkotter and S. Ruhrmann (2005). "Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia." Schizophr Res **73**(2-3): 297-310.
78. Brown, K. J., C. J. Gonsalvez, A. W. Harris, L. M. Williams and E. Gordon (2002). "Target and non-target ERP disturbances in first episode vs. chronic schizophrenia." Clin Neurophysiol **113**(11): 1754-1763.
79. Demiralp, T., A. Ucok, M. Devrim, U. Isoglu-Alkac, A. Tecer and J. Polich (2002). "N2 and P3 components of event-related potential in first-episode schizophrenic patients: scalp topography, medication, and latency effects." Psychiatry Res **111**(2-3): 167-179.
80. Salisbury, D. F., M. E. Shenton, A. R. Sherwood, I. A. Fischer, D. A. Yurgelun-Todd, M. Tohen and R. W. McCarley (1998). "First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe." Arch Gen Psychiatry **55**(2): 173-180.
81. Woodberry, K. A., W. R. McFarlane, A. J. Giuliano, M. B. Verdi, W. L. Cook, S. V. Faraone and L. J. Seidman (2013). "Change in neuropsychological functioning over one year in youth at clinical high risk for psychosis." Schizophr Res **146**(1-3): 87-94.
82. Fusar-Poli, P., G. Deste, R. Smieskova, S. Barlati, A. R. Yung, O. Howes, R. D. Stieglitz, A. Vita, P. McGuire and S. Borgwardt (2012). "Cognitive functioning in prodromal psychosis: a meta-analysis." Arch Gen Psychiatry **69**(6): 562-571.
83. Lewandowski, K. E., B. M. Cohen and D. Ongur (2011). "Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder." Psychol Med **41**(2): 225-241.
84. Johannesen, J. K., B. F. O'Donnell, A. Shekhar, J. H. McGrew and W. P. Hetrick (2013). "Diagnostic specificity of neurophysiological

endophenotypes in schizophrenia and bipolar disorder." Schizophr Bull **39**(6): 1219-1229.

85. Ethridge, L. E., J. P. Hamm, J. R. Shapiro, A. T. Summerfelt, S. K. Keedy, M. C. Stevens, G. Pearlson, C. A. Tamminga, N. N. Boutros, J. A. Sweeney, M. S. Keshavan, G. Thaker and B. A. Clementz (2012). "Neural activations during auditory oddball processing discriminating schizophrenia and psychotic bipolar disorder." Biol Psychiatry 72(9): 766-774.
86. Hall, M. H., J. W. Smoller, N. R. Cook, K. Schulze, P. Hyoun Lee, G. Taylor, E. Bramon, M. J. Coleman, R. M. Murray, D. F. Salisbury and D. L. Levy (2012). "Patterns of deficits in brain function in bipolar disorder and schizophrenia: a cluster analytic study." Psychiatry Res 200(2-3): 272-280.
87. Hamm, J. P., L. E. Ethridge, J. R. Shapiro, M. C. Stevens, N. N. Boutros, A. T. Summerfelt, M. S. Keshavan, J. A. Sweeney, G. Pearlson, C. A. Tamminga, G. Thaker and B. A. Clementz (2012). "Spatiotemporal and frequency domain analysis of auditory paired stimuli processing in schizophrenia and bipolar disorder with psychosis." Psychophysiology 49(4): 522-530.
88. Thaker, G. K. (2008). "Neurophysiological endophenotypes across bipolar and schizophrenia psychosis." Schizophr Bull 34(4): 760-773.
89. Light, G. A., M. A. Geyer, B. A. Clementz, K. S. Cadenhead and D. L. Braff (2000). "Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications." Am J Psychiatry 157(5): 767-771.

PAPER 1 SUPPLEMENTARY MATERIAL

Table 1. Oddball task EROs comparisons

Descriptive statistics

Group	Mean	SD	N
Controls	1.28	0.40	35
Early psychosis patients	0.94	0.37	34

Tests of between-subjects effects

Parameter	Sum Sq.	d.f.	Mean Sq.	F	Sig
clinical group	2.06	1	2.06	13.99	<0.001
Error	9.86	67	0.15		

Comparisons of mean group differences

Comparison	Estimated mean difference	SE of difference	Sig.	Adjusted 95% CI
Controls Vs Early psychosis patients	0.34	0.09	<0.001	0.16 to 0.53

EROs and age were log transformed for ANOVA comparisons.

Table 2. Passive oddball EROs comparisons

Descriptive statistics

Group	Mean	SD	N
Controls	0.45	0.19	35
Early psychosis patients	0.32	0.22	34

Tests of between-subjects effects

Parameter	'Sum Sq.'	'd.f.'	'Mean Sq.'	'F'	'Prob>F'
'clinical group'	0.32	1	0.32	7.20	0.009
'Error'	2.93	68	0.04		

Comparisons of mean group differences

Comparison	Estimated mean difference	SE of difference	Sig.	Adjusted 95% CI
Controls Vs Early psychosis patients	0.14	0.05	0.009	0.04 to 0.24

EROs and age were log transformed for ANOVA comparisons.

Table 3. Low frequency EROs gating comparisons

Descriptive statistics

Group	Mean	SD	N
Controls	-0.77	0.46	35
Early psychosis patients	-1.12	0.46	34

Tests of between-subjects effects

Parameter	'Sum Sq.'	'd.f.'	'Mean Sq.'	'F'	'Prob>F'
'clinical group' * 'age'	0.84	1	0.84	4.56	0.04
'clinical group'	0.43	1	0.43	2.36	0.13
'age'	1.02	1	1.02	5.23	0.02
'Error'	11.98	65	0.18		

Parameter estimates

Parameter	B (SE)	t	Sig	95% CI
Early psychosis patients * age	-0.003 (0.02)	-0.15	0.88	-0.04 to 0.03
Controls * age	-0.06 (0.02)	-3.30	0.002	-0.09 to -0.02

Comparisons of mean group differences

Comparison	Estimated mean difference	SE of difference	Sig.	Adjusted 95% CI
Controls Vs Early psychosis patients	-0.35	0.10	0.001	-0.56 to -0.14

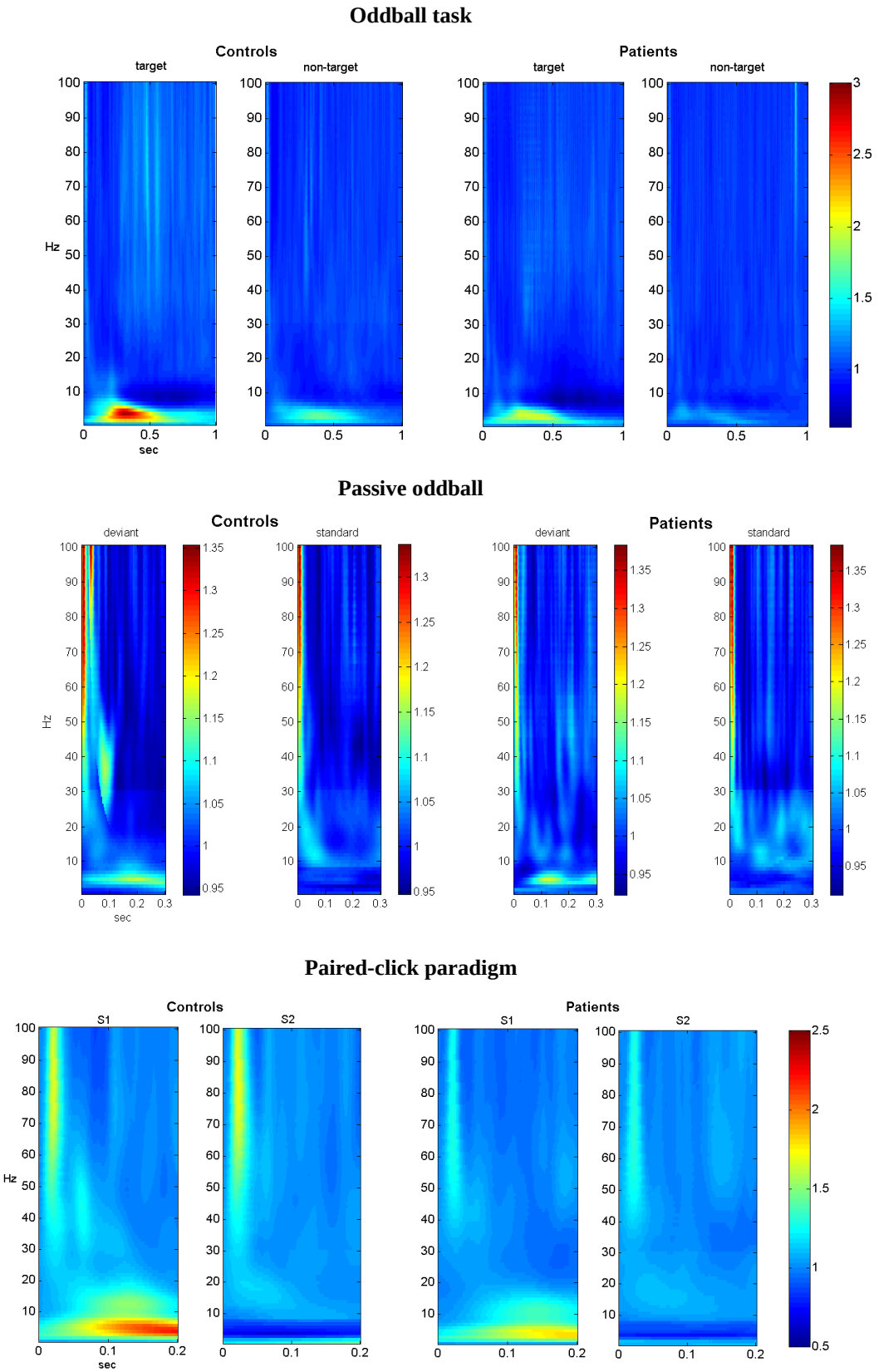
EROs gating ratio was log transformed for ANOVA comparisons.

Table 4. Relationship between EROs, illness duration and PANSS scores

EROs cluster	**Bivariate correlations (Sig.)**	**Multivariate analysis**				
		Adjusted R Square	**ANOVA F (Sig.)**	**Std Beta**	**t**	**Sig.**
Illness duration[a]						
Oddball task EROs	0.49 (< 0.01)					
Low freq. EROs gating	0.47 (< 0.01)					
		0.26 (0.28)	12.38 (p= 0.001)			
(Constant)	-			-	0.56	0.58
Oddball task EROs				0.53	3.52	0.001
Low freq. EROs gating						
PANSS negative symptoms[b]						
		0.51 (0.47)	15.15 (< 0.001)			
(Constant)	-			-	-2.09	0.04
Low freq. EROs gating	0.54 (0.001)			0.47	3.55	0.001
High freq. EROs gating	0.55 (0.001)			0.47	3.60	0.001

a) Passive oddball EROs showed no significant bivariate correlation with illness duration and were excluded from the regression analysis.Oddball task EROs and Low fre. EROs gating were not independent predictors of illness duration, the ratio between the two provided the best fit in the regression model. **b)** oddball task and passive oddball EROs showed no significant bivariate correlations with PANSS negative symptoms score and did not fit in the regression model using this score as dependent variable. High frequency EROs gating was then entered together with low frequency EROs gating, the two measures independently predicting PANSS negative symptoms. The studied EROs showed no significant association with PANSS positive symptoms score.

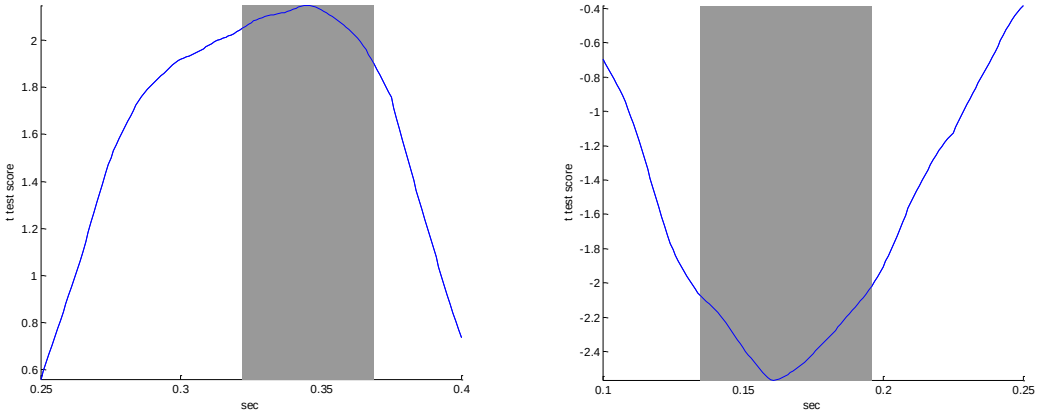
Appendix figure 1. EROs plots



Appendix figure 1. EROs plots for the two stimuli types in each of the tested paradigms. EROs represent power change in relation to baseline.

Appendix figure 2. ERP comparisons

a) P300 ERP (Pz) - controls Vs patients **b) MMN ERP (Fz) - controls Vs patients**



Appendix figure 2. a) and b) P300 and MMN ERP amplitude comparisons between controls and patients, for a 250-400 ms and a 100-250 ms post stimulus time windows, respectively. T test scores (y-axis) are displayed and the shaded area represents statistical significant difference, $p<.05$, corrected for multiple comparisons.

APPENDICES

Appendix One

Information and Questionnaires provided to study participants

Before each participant received their clinical assessment and EEG test, the following material was provided to them to read and complete:

- **Maudsley Family Study participant information sheet**
- **Information sheet provided on day of testing**
- **Consent form one - consent to take part**
- **Study questionnaire**

A1.1 Maudsley Family Study participant information sheet

Institute of Psychiatry

at The Maudsley

KING'S College LONDON

University of London

PATIENT INFORMATION SHEET

MAUDSLEY FAMILY PSYCHOSIS STUDY

You are invited to take part in a new research project at the Institute of Psychiatry.

Why have I been contacted?

This research is a continuation of the Maudsley Family Psychosis Study, which has investigated brain structure and function in people with psychosis and their relatives.

Before you decide to take part it is important that you understand why the research is being done and what it involves. Please read through this information sheet carefully. You may like to discuss this research with friends or family. Please feel free to contact us if you have any questions.

Why are we doing this research?

This study seeks to find out more about the genes that are involved in predisposing to schizophrenia and the way in which these relate to the functioning of the brain. We do this by comparing brain structure and function of people with schizophrenia to that of their relatives and to members of the general population. We hope that our research will help future treatments and lead to an earlier diagnosis of schizophrenia.

Do I have to take part?

Participation in the study is entirely voluntary. If you do not wish to participate in the study, any care that you are receiving will not be affected. If you agree to take part in this study and later wish to withdraw, you may do so at any time without giving a reason. If you decide to withdraw, your future treatment will not be affected.

If you would be happy to take part, then you will be given a copy of this information sheet, and we will ask you to sign a consent form.

How long will it take?

We would like you to come to the Institute of Psychiatry in London, on a date which is convenient for you. Typically you would only need to come to London to see us once. The research would be *completed within one day*. We are also very happy for you to take part in the research with other family members on the same day.

Costs

We will reimburse all travel expenses and provide refreshments while you are here. We will also cover any other expenses incurred due to participation in the study, such as overnight accommodation or child care. We also provide further compensation for any inconvenience caused.

Many thanks for taking the time to consider taking part. Next is an explanation of what is involved in this research study.

(1) EVOKED POTENTIALS:

Evoked Potentials (EPs) are aimed to record brain electrical activity in order to understand more about brain function. They are based in a test called EEG (Electroencephalogram) that is done routinely in most hospitals. It is also similar to an ECG test, only leads are attached to the head instead of the chest. The procedure involves attaching some leads on your head to record the electrical waves that naturally take place in the brain. We will look at how your brain activity changes when you listen to sounds. This test takes about *2 hours*. It does not involve any radiation and cannot hurt you in any way.

(2) DNA: A cheek swab or blood sample is taken for genetic testing. DNA or hereditary material is extracted from the blood and is added to a panel of several other samples, which are then examined to see if we can identify genes that contribute to schizophrenia. We are interested in how specific genes affect how the brain functions and the structure that it has. There is no individual result from this test.

(3) PSYCHOLOGICAL INTERVIEW: The interview will concentrate on your past medical history and how any psychological symptoms developed over time. It lasts for about *one hour*.

What are the possible benefits of taking part?

There will be no immediate benefit to you from this project but we hope it will increase our understanding of how the brain functions in schizophrenia and the role of certain genes. In this way, we hope to improve the future treatment and early diagnosis of schizophrenia.

Confidentiality

The measurements from the various tests will be combined with those from other participants and analysed on computers at the Institute of Psychiatry. All results of the tests are absolutely confidential and are protected by the Data Protection Act. There will be no specific 'results' from your tests so you will not be contacted in the future, although we can provide general information on our progress and research. If, during the course of this project, we obtain information that will be clinically important, we will seek your approval to contact your GP.

Complaints

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (020 7848 0565). If you remain unhappy and wish to complain formally, you can do this through The Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee.

Harm

In the extremely unlikely event that something does go wrong during this research project and you are harmed you may have grounds for a legal action for compensation against King's College London.

What will happen to the results from the research?

You will be kept informed of the progress of the Maudsley Family Psychosis Study research by the regular sending of newsletters. Any results from the current study will be communicated to other health professionals and researchers through conference presentations and academic journals. Participants will not be identifiable in any research publications.

Ethical Approval

The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics committee have reviewed this research and given ethical approval.

Many thanks for reading this information sheet. We hope that you will agree to take part.

Contact Details

If you would like to take part or if you have any questions, please contact Miguel Constante.

Post : Miguel Constante
Division of Psychological Medicine
P063
Institute of Psychiatry
De Crespigny Park
London, SE5 8AF
Phone: +4407904413299
Email: miguel.constante@kcl.ac.uk

A1.2 Information sheet provided in day of testing

Institute of Psychiatry

at The Maudsley

KING'S College LONDON

University of London

A STUDY OF BRAIN FUNCTION USING EEG SCANS

You have been asked here to take part in a study conducted by Miguel Constante, Ian Williams, Madiha Shaikh, Dr. Elvira Bramon and Prof. Robin Murray. We are hoping to learn more about mental functioning in health and in those living with psychological illness. We would like to invite you to take part in the following tests.

CLINICAL INTERVIEW

This is a standard medical interview. You will be asked you about your past medical history and how any psychological symptoms developed over time. It lasts about one hour.

EEG TEST

This test involves recording electrical waves that occur naturally in the brain. It is like an ECG test for the heart, only in this case leads are attached to the head instead of the chest. We will do the EEG whilst you are doing a series of simple tasks which involve listening to tones through earphones and responding to them. The test can not hurt you in any way and it does not use any radiation. The EEG test takes about 90 minutes.

BLOOD TEST

A blood sample is taken for genetic testing. DNA or hereditary material is extracted from the blood and is added to a panel of several other samples. Then they are examined to see if we can identify genes that contribute to mental disorders. There is no individual result from this test. The DNA you donate will be stored in our laboratory as an anonymous sample (with a code, not with your name). This will allow us to do further studies in the future keeping up with developments in the field. Every future study will have to be approved by the Ethical Committee. The blood test only takes a couple of minutes.

Finally, please take this into account: You have the right to choose whether or not you want to participate in this project. There will be no immediate benefit to you from this project but it may prove of benefit in the understanding of how the brain functions in psychological illness. Participation in the study is entirely voluntary. If you agree to take part in this study and later wish to withdraw, you may do so at any time without giving a reason. The results of the test are confidential and are protected by the Data Protection Act. You will not be identified in our computer by name but by a number. The results will only be used to understand more about mental functioning in people living with psychological problems.

A1.3 Consent Form

Institute of Psychiatry

at The Maudsley

KING'S College LONDON

University of London

A STUDY OF BRAIN FUNCTION IN PSYCHOSIS

CONSENT FORM

I _____

(Please print name in capital letters)

of _____

_____

_____

_____

(Please write address in capital letters)

have read the information sheet for the above research project.

I understand the purpose of the project and that I am perfectly free to take part or not as I wish. The research project has been explained to me and all my questions answered to my satisfaction.

In light of what I have now been told, I freely consent to take part in the research project.

These are the details of my General Practitioner:

Dr. _____

Surgery_____

Address_____

_____

_____

Signature of participant: _____

Date: _____

A1.4 Study questionnaire

Any information that you give will be treated as strictly confidential

Name:	
Date of Birth:	**Today's date:**
Please circle your handedness: **Right handed / left handed / use both hands**	
Please list any medications that you take on a regular basis **Medications:** **Daily dose:**	

Please tick your completed level of education:

None	
GCSE's / O-Levels	
GNVQ / B-TEC	
AS Levels / A1	
A Levels / A2	
Degree	
Post Graduate Degree	
Other (Please Specify)	

Total years of full time education: _____

Occupation: _____

Substance Use Questionnaire					
Tobacco	How many cigarettes a day do you smoke currently?				
	At what time did you smoke your last cigarette today?				
	What is your average daily number over the last month?				
	How many years have you been smoking for?				
Cannabis	When did you smoke cannabis for the last time?				
	What is the average you take in one day currently? (Number of joints per day)				
Alcohol	What is the average amount of alcohol you take per day? (You can use units or explain the number of glasses of each drink)				
	How much per day during the working week?				
	How much per day during the weekend?				
DRUG	**Never used**	**Occasional Use**	**Weekly Use**	**Last time Used was on…**	**Amount used on average**
Amphetamine or Speed					
LSD					
Ecstasy					
Solvents (glue)					
Heroin					
Cocaine					

Appendix Two- EEG Data Collection – Supplementary Material

This appendix supplements the methodology section (Chapter Two) and aims to provide fuller and more specific details regarding the methods of EEG data collection.

A2.1 Data collection – general laboratory information

New EEG recordings undertaken as part of my own data collection were carried out at the Neurophysiology Laboratory in the Psychosis Centre of the Institute of Psychiatry, King's College London. The EEG recordings of previously collected data by my colleagues and which were also used in this thesis, were carried out in the Electrophysiology Laboratory inside The Eric Byers Magnetic Resonance Suite of Mapother House, King's College Hospital. The move between labs took place in February 2007.

The stimuli for each paradigm did not change between the laboratories and were generated and presented in the same manner, using the STIM stimulus presentation system *(Compumedics Neuroscan, Texas, USA)* though intra-aural earphones *(ER3-14A Eartips for ER-3 and ER-5, Etymotic Research Inc. Illinois, USA)*. The electroencephalogram (EEG) was recorded using the SCAN software package *(Compumedics Neuroscan, Texas, USA)* and in 2007 the software was updated from version 4.2 to version 4.3.

In the Mapother House laboratory a 64-channel SynAmps® (Model 5083) amplifier was used, while in the Psychosis Centre the SynAmps® was upgraded to the SCAN NuAmps Express™ 40-channel monopolar digital amplifier (pictured on the right of figure A3). The NuAmps was quicker and easier to set up for recording, which proved to be especially advantageous when dealing with participants who were particularly unwell or impatient. As a result of the change in amplifier a different EEG cap was used in the new facility.

In the Mapother House neurophysiology laboratory data were collected using a 64-channel EEG Quik-Cap fitted with silver/silver-chloride electrodes *(Compumedics Neuroscan, Texas, USA)* referenced to the mastoids and positioned according to the 10/20 International System. In spring 2007 the move to the Psychosis Centre and the NuAmps system necessitated the use of a 40-channel Quik-Cap. The channel layouts of these two caps can be seen in figures A1 and A2, and the referencing to linked mastoids used in the new laboratory can be seen on the left of figure A3.

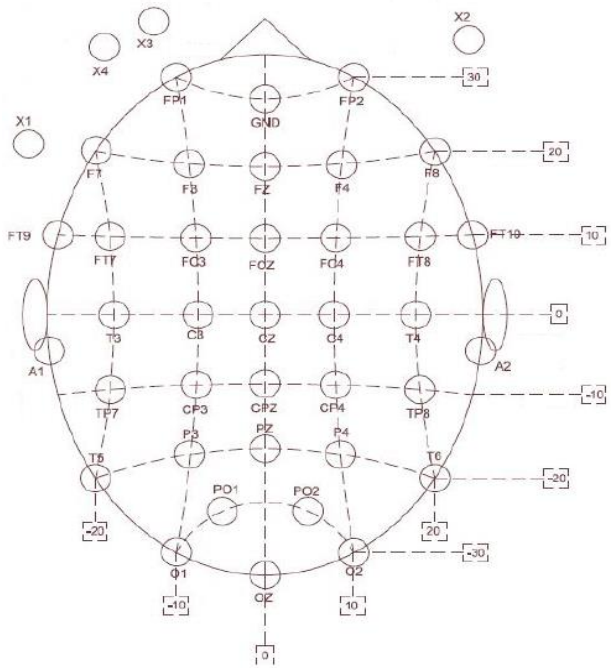


Figure A1: Layout of 40 channel Quik-Cap

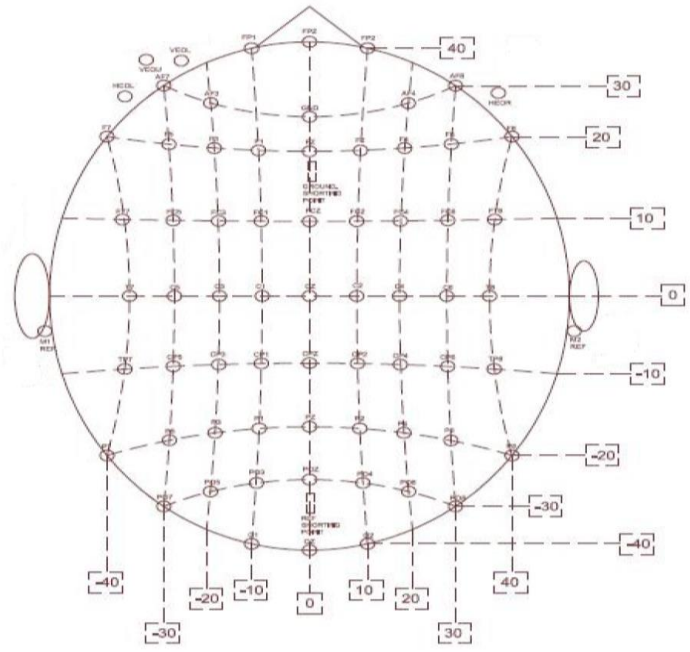


Figure A2: Layout of 64 channel Quik-Cap

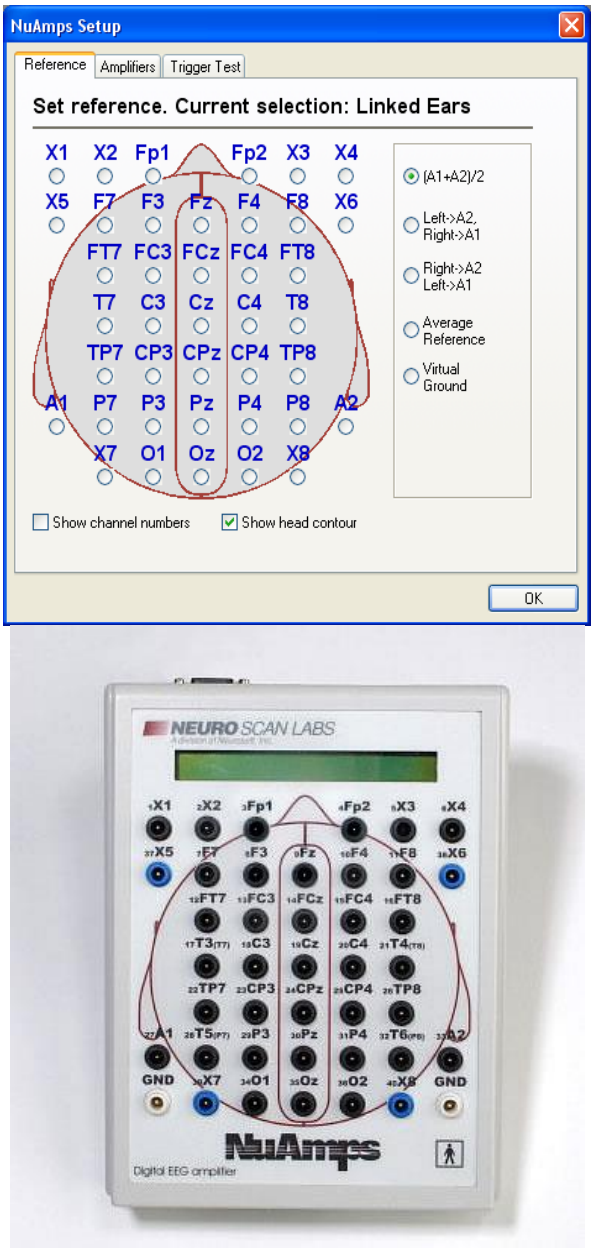


Figure A3: EEG referencing

In all recordings FPZ (mid-forehead) served as ground and impedances were kept below 5 kΩ at all sites with the use of conductive gel *(ECI Electrogel™, Electro-Cap International Inc. Ohio, USA).* A small amount of gel was applied to the scalp through holes in each electrode using 10 ml syringes *(BD 10 ml Syringe with Luer-Lok™ tip, Becton Dickson & Co., NJ, USA)* fitted with blunt needles (*BD 16G¾ Blunt Square Grind PrescisionGlide® Needle, Becton Dickson & Co., NJ, USA)*. The needles were then used to gently manipulate the hair until the impedance at each electrode fell below the desired level. An example of the change in impedances across the scalp that was

required before commencing testing can be seen below in figure A4. This process would usually take around ten minutes to complete.

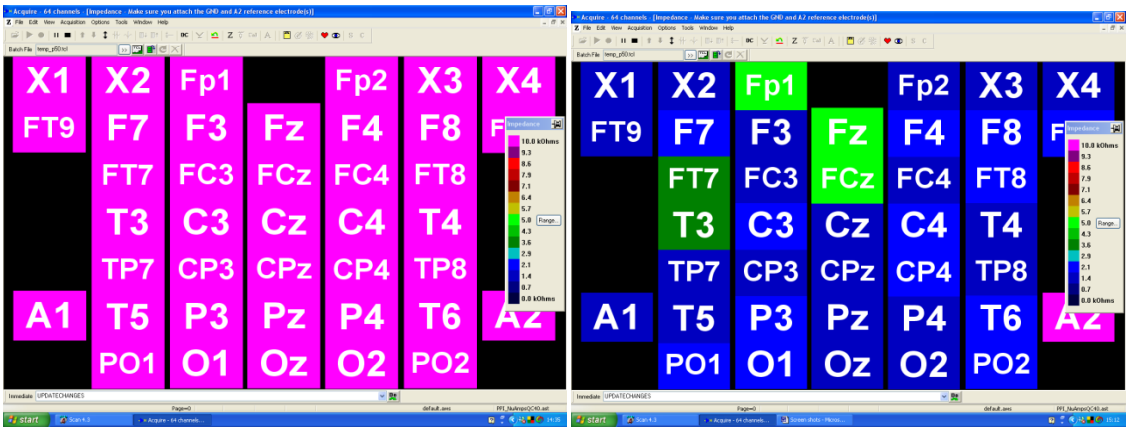


Figure A4: Impedance screens: before and after preparation shots

Monitoring of the blinks and eye movement was achieved by recording of electromyographic (EMG) activity from electro-oculogram (EOG) electrodes placed at four locations (the outer canthus of each eye, and above and below the right eye over the orbicularis oculi) as shown in figure seventy-three. With the 64-channel cap $_{V}EOG_{U}$ and $_{V}EOG_{L}$ (the upper and lower vertical electro-oculogram electrodes) were placed above and below the right eye, and $_{H}EOG_{L}$ and $_{H}EOG_{R}$ (left and right horizontal electro-oculogram electrodes) to the outer canthus of the left and right eyes respectively. With the 40-channel Quik-Cap, electrodes X_1 and X_2 were placed above and below the right eye respectively, while X_3 and X_4 were placed to the left and right of the eyes.

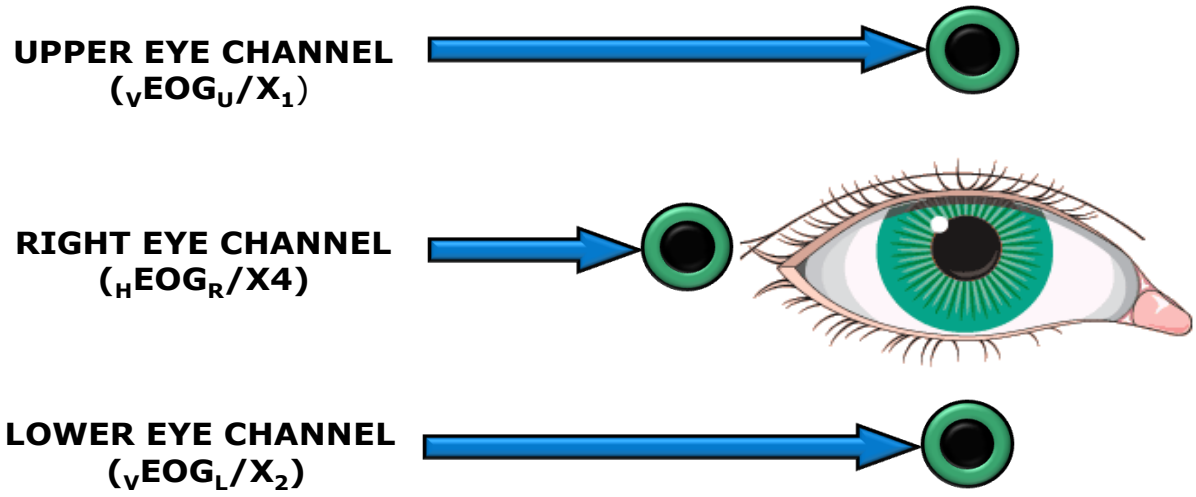


Figure A5: Placement of electro-oculogram electrodes at right eye

To prepare the areas on the face and mastoids for the placement of electrodes, abrasive gel was gently applied to the skin *(NuPrep Abrasive Skin Prepping Gel, D.O Weaver and Co., Colorado, USA)*, and this was then cleansed with an alcohol swab *(70% Isopropyl Alcohol Alcotip Swab, Universal Hospital Supplies Ltd., UK)*. This process reduces the impedance between skin surface and conductive gel by removing makeup, skin oil and dead skin cells. As with the cap electrodes, with the reference and EOG electrodes impedances below 5 kΩ were required.

Each recording session lasted approximately 45 minutes and the neurophysiological paradigms were carried out in a fixed order: 1st - paired-clicks, 2nd auditory oddball task and 3rd. passive oddball (these were followed by recording of the resting EEG and PPI paradigm, which were not subject of study in this thesis). Participants were seated in a comfortable chair throughout. They were asked to sit as still and quietly as possible, to keep their eyes open and to concentrate on the task at hand. It was also ensured that the patient was not chewing gum during testing to avoid muscle artefacts in the recording.

Before setting up the EEG cap the participant was talked through what to expect from the session in detail, allowed to examine the cap and gel, and was given ample opportunity to ask any questions. They then gave informed written consent on the form shown in appendix one (sections A1.3).

A2.2 Differences in data collection between the two labs involved

While I personally collected data from only one laboratory, this thesis includes data collected in one other laboratory and using slightly different data collection techniques. A detailed survey of data collection methodology for the sensory gating, passive oddball and oddball task paradigms over the two labs can be seen in table A1.

The change reflected the continuous updating of the amplifier and the version of the SCAN software used. The high pass filter on the previous amplifier would only go as far as 0.05 Hz, but the most recent NuAmps amplifier can handle DC so this was chosen. Other points such as the references used and the filters applied during collection are relatively minor and in no way affect the compatibility of the continuous EEG data. With all the EEG paradigms studied here, while all data are fully compatible, differences in lab are of course included as covariates in all analyses of EROs/ERPs.

Table A1: Sensory gating, passive oddball and oddball task paradigms data collection methodology

Laboratory	Researcher (Years)	N Participants included in this thesis	Paradigms measured	Software	System/ Amplifiers	Electrodes	Eye measured	Digitised (A/D rate)	Notch Filter	Filters Low Pass/ High Pass	References
Eric Byers Magnetic Resonance Suite, Mapother House	Dr Elvira Bramon (2001-2005) Ian Williams (2005-2007)	EB 39 IW 87	sensory gating, passive oddball and oddball task	SCAN 4.2	NeuroScan SynAmps	64 Channel QuickCap	Right	1000 Hz	50 Hz	100Hz 0.05Hz (24 dB/octave roll-off).	Bilateral Mastoids
Neurophysiology Laboratory, Psychosis Centre, Institute of Psychiatry	Miguel Constante, Ian Williams, Madiha Shaikh (2007-2010)	MC 70 IW & MS 65	sensory gating, passive oddball and oddball task	SCAN 4.3	NeuroScan NuAmps	40 Channel QuickCap	Right	1000 Hz	None	100Hz DC (24 dB/octave roll-off)	Linked Mastoids

REFERENCES

Adler, L. E., L. D. Hoffer, A. Wiser and R. Freedman (1993). "Normalization of auditory physiology by cigarette smoking in schizophrenic patients." Am J Psychiatry 150(12): 1856-1861.

Albrecht, M. A., G. Price, J. Lee, R. Iyyalol and M. T. Martin-Iverson (2012). "Dexamphetamine reduces auditory P3 delta power and phase-locking while increasing gamma power." Eur Neuropsychopharmacol 22(10): 734-746.

Allen, A. J., M. E. Griss, B. S. Folley, K. A. Hawkins and G. D. Pearlson (2009). "Endophenotypes in schizophrenia: a selective review." Schizophr Res 109(1-3): 24-37.

Altman, E. G., D. Hedeker, J. L. Peterson and J. M. Davis (1997). "The Altman Self-Rating Mania Scale." Biol Psychiatry 42(10): 948-955.

Arnone, D., J. Cavanagh, D. Gerber, S. M. Lawrie, K. P. Ebmeier and A. M. McIntosh (2009). "Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis." Br J Psychiatry 195(3): 194-201.

Baker, K., T. Baldeweg, S. Sivagnanasundaram, P. Scambler and D. Skuse (2005). "COMT Val108/158 Met modifies mismatch negativity and cognitive function in 22q11 deletion syndrome." Biol Psychiatry 58(1): 23-31.

Barch, D. M., J. Bustillo, W. Gaebel, R. Gur, S. Heckers, D. Malaspina, M. J. Owen, S. Schultz, R. Tandon, M. Tsuang, J. Van Os and W. Carpenter (2013). "Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: Relevance to DSM-5." Schizophr Res 150(1): 15-20.

Barr, M. S., F. Farzan, L. C. Tran, R. Chen, P. B. Fitzgerald and Z. J. Daskalakis (2010). "Evidence for excessive frontal evoked gamma oscillatory activity in schizophrenia during working memory." Schizophr Res. 121(1-3): 146-152. doi: 110.1016/j.schres.2010.1005.1023. Epub 2010 Jul 1013.

Barry, R. J., A. R. Clarke, S. J. Johnstone, R. McCarthy and M. Selikowitz (2009). "Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes." Biol Psychiatry 66(4): 398-401.

Basar, E., C. Basar-Eroglu, S. Karakas and M. Schurmann (2001). "Gamma, alpha, delta, and theta oscillations govern cognitive processes." Int J Psychophysiol 39(2-3): 241-248.

Basar, E. and B. Guntekin (2008). "A review of brain oscillations in cognitive disorders and the role of neurotransmitters." Brain Res 1235: 172-193.

Basar, E. and B. Guntekin (2013). "Review of delta, theta, alpha, beta, and gamma response oscillations in neuropsychiatric disorders." Suppl Clin Neurophysiol 62: 303-341.

Beck, A. T., C. H. Ward, M. Mendelson, J. Mock and J. Erbaugh (1961). "An inventory for measuring depression." Arch Gen Psychiatry 4: 561-571.

Bernat, E. M., S. M. Malone, W. J. Williams, C. J. Patrick and W. G. Iacono (2007). "Decomposing delta, theta, and alpha time-frequency ERP activity from a visual oddball task using PCA." Int J Psychophysiol 64(1): 62-74.

Blackwood, D. H., A. Fordyce, M. T. Walker, D. M. St Clair, D. J. Porteous and W. J. Muir (2001). "Schizophrenia and affective disorders--cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family." Am J Hum Genet 69(2): 428-433.

Bora, E., A. Fornito, J. Radua, M. Walterfang, M. Seal, S. J. Wood, M. Yucel, D. Velakoulis and C. Pantelis (2011). "Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis." Schizophr Res. 127(1-3): 46-57. doi: 10.1016/j.schres.2010.1012.1020.

Boutros, N. N., C. Arfken, S. Galderisi, J. Warrick, G. Pratt and W. Iacono (2008). "The status of spectral EEG abnormality as a diagnostic test for schizophrenia." Schizophr Res 99(1-3): 225-237.

Boutros, N. N., A. Brockhaus-Dumke, K. Gjini, A. Vedeniapin, M. Elfakhani, S. Burroughs and M. Keshavan (2009). "Sensory-gating deficit of the N100 mid-latency auditory evoked potential in medicated schizophrenia patients." Schizophr Res 113(2-3): 339-346.

Bozikas, V. P. and C. Andreou (2011). "Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature." Aust N Z J Psychiatry 45(2): 93-108.

Braff, D. L., R. Freedman, N. J. Schork and Gottesman, II (2007). "Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder." Schizophr Bull 33(1): 21-32.

Bramon, E., R. J. Croft, C. McDonald, G. K. Virdi, J. G. Gruzelier, T. Baldeweg, P. C. Sham, S. Frangou and R. M. Murray (2004). "Mismatch negativity in schizophrenia: a family study." Schizophr Res 67(1): 1-10.

Bramon, E., E. Dempster, S. Frangou, C. McDonald, P. Schoenberg, J. H. MacCabe, M. Walshe, P. Sham, D. Collier and R. M. Murray (2006). "Is there an association between the COMT gene and P300 endophenotypes?" Eur Psychiatry 21(1): 70-73.

Bramon, E., E. Dempster, S. Frangou, M. Shaikh, M. Walshe, F. M. Filbey, C. McDonald, P. Sham, D. A. Collier and R. Murray (2008). "Neuregulin-1 and the P300 waveform--a preliminary association study using a psychosis endophenotype." Schizophr Res 103(1-3): 178-185.

Bramon, E., C. McDonald, R. J. Croft, S. Landau, F. Filbey, J. H. Gruzelier, P. C. Sham, S. Frangou and R. M. Murray (2005). "Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study." Neuroimage 27(4): 960-968.

Bramon, E., M. Pirinen, A. Strange, K. Lin, C. Freeman, C. Bellenguez, Z. Su, G. Band, R. Pearson, D. Vukcevic, C. Langford, P. Deloukas, S. Hunt, E. Gray, S. Dronov, S. C. Potter, A. Tashakkori-Ghanbaria, S. Edkins, S. J. Bumpstead, M. J. Arranz, S. Bakker, S. Bender, R. Bruggeman, W. Cahn, D. Chandler, D. A. Collier, B. Crespo-Facorro, P. Dazzan, L. de Haan, M. Di Forti, M. Dragovic, I. Giegling, J. Hall, C. Iyegbe, A. Jablensky, R. S. Kahn, L. Kalaydjieva, E. Kravariti, S. Lawrie, D. H. Linszen, I. Mata, C. McDonald, A. McIntosh, I. Myin-Germeys, R. A. Ophoff, C. M. Pariante, T. Paunio, M. Picchioni, S. Ripke, D. Rujescu, H. Sauer, M. Shaikh, J. Sussmann, J. Suvisaari, S. Tosato, T. Toulopoulou, J. Van Os, M. Walshe, M. Weisbrod, H. Whalley, D. Wiersma, J. M. Blackwell, M. A. Brown, J. P. Casas, A. Corvin, A. Duncanson, J. A. Jankowski, H. S. Markus, C. G. Mathew, C. N. Palmer, R. Plomin, A. Rautanen, S. J. Sawcer, R. C. Trembath, N. W. Wood, I. Barroso, L. Peltonen, C. M. Lewis, R. M. Murray, P. Donnelly, J. Powell and C. C. Spencer (2014). "A genome-wide association analysis of a broad psychosis phenotype identifies three loci for further investigation." Biol Psychiatry 75(5): 386-397.

Bramon, E., S. Rabe-Hesketh, P. Sham, R. M. Murray and S. Frangou (2004). "Meta-analysis of the P300 and P50 waveforms in schizophrenia." Schizophr Res 70(2-3): 315-329.

Bramon, E., M. Shaikh, M. Broome, J. Lappin, D. Berge, F. Day, J. Woolley, P. Tabraham, M. Madre, L. Johns, O. Howes, L. Valmaggia, V. Perez, P. Sham, R. M. Murray and P. McGuire (2008). "Abnormal P300 in people with high risk of developing psychosis." Neuroimage 41(2): 553-560.

Bramon, E. and P. C. Sham (2001). "The common genetic liability between schizophrenia and bipolar disorder: a review." Curr Psychiatry Rep 3(4): 332-337.

Brenner, C. A., P. D. Kieffaber, B. A. Clementz, J. K. Johannesen, A. Shekhar, B. F. O'Donnell and W. P. Hetrick (2009). "Event-related potential abnormalities in schizophrenia: a failure to "gate in" salient information?" Schizophr Res 113(2-3): 332-338.

Brockhaus-Dumke, A., R. Mueller, U. Faigle and J. Klosterkoetter (2008). "Sensory gating revisited: relation between brain oscillations and auditory evoked potentials in schizophrenia." Schizophr Res 99(1-3): 238-249.

Brockhaus-Dumke, A., F. Schultze-Lutter, R. Mueller, I. Tendolkar, A. Bechdolf, R. Pukrop, J. Klosterkoetter and S. Ruhrmann (2008). "Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients." Biol Psychiatry 64(5): 376-384.

Brockhaus-Dumke, A., I. Tendolkar, R. Pukrop, F. Schultze-Lutter, J. Klosterkotter and S. Ruhrmann (2005). "Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia." Schizophr Res 73(2-3): 297-310.

Brown, K. J., C. J. Gonsalvez, A. W. Harris, L. M. Williams and E. Gordon (2002). "Target and non-target ERP disturbances in first episode vs. chronic schizophrenia." Clin Neurophysiol 113(11): 1754-1763.

Buzsaki, G. and A. Draguhn (2004). "Neuronal oscillations in cortical networks." Science 304(5679): 1926-1929.

Buzsaki, G. and B. O. Watson (2012). "Brain rhythms and neural syntax: implications for efficient coding of cognitive content and neuropsychiatric disease." Dialogues Clin Neurosci 14(4): 345-367.

Calkins, M. E., D. J. Dobie, K. S. Cadenhead, A. Olincy, R. Freedman, M. F. Green, T. A. Greenwood, R. E. Gur, R. C. Gur, G. A. Light, J. Mintz, K. H. Nuechterlein, A. D. Radant, N. J. Schork, L. J. Seidman, L. J. Siever, J. M. Silverman, W. S. Stone, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang, B. I. Turetsky and D. L. Braff (2007). "The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration." Schizophr Bull 33(1): 33-48.

Cannon, T. D. and M. C. Keller (2006). "Endophenotypes in the genetic analyses of mental disorders." Annu Rev Clin Psychol 2: 267-290.

Cannon, T. D., T. G. van Erp, C. E. Bearden, R. Loewy, P. Thompson, A. W. Toga, M. O. Huttunen, M. S. Keshavan, L. J. Seidman and M. T. Tsuang (2003). "Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions." Schizophr Bull 29(4): 653-669.

Canolty, R. T. and R. T. Knight (2010). "The functional role of cross-frequency coupling." Trends Cogn Sci 14(11): 506-515.

Cardno, A. G., F. V. Rijsdijk, P. C. Sham, R. M. Murray and P. McGuffin (2002). "A twin study of genetic relationships between psychotic symptoms." Am J Psychiatry 159(4): 539-545.

Chan, R. C., X. Di, G. M. McAlonan and Q. Y. Gong (2011). "Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression." Schizophr Bull 37(1): 177-188.

Chen, K. C., I. H. Lee, Y. K. Yang, S. Landau, W. H. Chang, P. S. Chen, R. B. Lu, A. S. David and E. Bramon (2013). "P300 waveform and dopamine transporter availability: a controlled EEG and SPECT study in medication-naive patients with schizophrenia and a meta-analysis." Psychol Med: 1-12.

Cho, R. Y., R. O. Konecky and C. S. Carter (2006). "Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia." Proc Natl Acad Sci U S A 103(52): 19878-19883.

Clementz, B. A., L. D. Blumenfeld and S. Cobb (1997). "The gamma band response may account for poor P50 suppression in schizophrenia." Neuroreport 8(18): 3889-3893.

Clementz, B. A., M. A. Geyer and D. L. Braff (1998). "Poor P50 suppression among schizophrenia patients and their first-degree biological relatives." Am J Psychiatry 155(12): 1691-1694.

Cobb, S. R., E. H. Buhl, K. Halasy, O. Paulsen and P. Somogyi (1995). "Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons." Nature 378(6552): 75-78.

Cobia, D. J., M. J. Smith, L. Wang and J. G. Csernansky (2012). "Longitudinal progression of frontal and temporal lobe changes in schizophrenia." Schizophr Res 139(1-3): 1-6.

Cohen, M. X. (2008). "Assessing transient cross-frequency coupling in EEG data." J Neurosci Methods 168(2): 494-499.

Corbetta, M. and G. L. Shulman (2002). "Control of goal-directed and stimulus-driven attention in the brain." Nat Rev Neurosci 3(3): 201-215.

Cornblatt, B. A., T. Lencz, C. W. Smith, C. U. Correll, A. M. Auther and E. Nakayama (2003). "The schizophrenia prodrome revisited: a neurodevelopmental perspective." Schizophr Bull 29(4): 633-651.

Coull, J. T. (1998). "Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology." Prog Neurobiol 55(4): 343-361.

Craddock, N. and M. J. Owen (2010). "The Kraepelinian dichotomy - going, going... but still not gone." Br J Psychiatry 196(2): 92-95.

Crow, T. J. (1990). "The continuum of psychosis and its genetic origins. The sixty-fifth Maudsley lecture." The British Journal of Psychiatry 156(6): 788-797.

Davies, P. L., W. P. Chang and W. J. Gavin (2009). "Maturation of sensory gating performance in children with and without sensory processing disorders." Int J Psychophysiol 72(2): 187-197.

De Vico Fallani, F., A. Maglione, F. Babiloni, D. Mattia, L. Astolfi, G. Vecchiato, A. De Rinaldis, S. Salinari, E. Pachou and S. Micheloyannis (2010). "Cortical network analysis in patients affected by schizophrenia." Brain Topogr. 23(2): 214-220. doi: 210.1007/s10548-10010-10133-10542. Epub 12010 Jan 10522.

de Wilde, O. M., L. J. Bour, P. M. Dingemans, J. H. Koelman, T. Boeree and D. H. Linszen (2008). "P300 deficits are present in young first-episode patients with schizophrenia and not in their healthy young siblings." Clin Neurophysiol 119(12): 2721-2726.

de Wilde, O. M., L. J. Bour, P. M. Dingemans, J. H. Koelman and D. H. Linszen (2007). "A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups." Schizophr Res 97(1-3): 137-151.

Delorme, A. and S. Makeig (2004). "EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis." J Neurosci Methods 134(1): 9-21.

Demiralp, T., C. S. Herrmann, M. E. Erdal, T. Ergenoglu, Y. H. Keskin, M. Ergen and H. Beydagi (2007). "DRD4 and DAT1 polymorphisms modulate human gamma band responses." Cereb Cortex 17(5): 1007-1019.

Demiralp, T., A. Ucok, M. Devrim, U. Isoglu-Alkac, A. Tecer and J. Polich (2002). "N2 and P3 components of event-related potential in first-episode schizophrenic patients: scalp topography, medication, and latency effects." Psychiatry Res 111(2-3): 167-179.

Dias, E. C., P. D. Butler, M. J. Hoptman and D. C. Javitt (2011). "Early sensory contributions to contextual encoding deficits in schizophrenia." Arch Gen Psychiatry 68(7): 654-664.

Diez, A., C. Cieza-Borrella, V. Suazo, R. Gonzalez-Sarmiento, S. Papiol and V. Molina (2014). "Cognitive outcome and gamma noise power unrelated to neuregulin 1 and 3 variation in schizophrenia." Ann Gen Psychiatry 13: 18.

Doege, K., A. T. Bates, T. P. White, D. Das, M. P. Boks and P. F. Liddle (2009). "Reduced event-related low frequency EEG activity in schizophrenia during an auditory oddball task." Psychophysiology 46(3): 566-577.

Donkers, F. C., S. R. Schwikert, A. M. Evans, K. M. Cleary, D. O. Perkins and A. Belger (2011). "Impaired neural synchrony in the theta frequency range in adolescents at familial risk for schizophrenia." Front Psychiatry 2: 51.

Dutt, A., T. Ganguly, M. Shaikh, M. Walshe, K. Schulze, N. Marshall, M. Constante, C. McDonald, R. M. Murray, M. P. Allin and E. Bramon (2012). "Association between hippocampal volume and P300 event related potential in psychosis: support for the Kraepelinian divide." Neuroimage 59(2): 997-1003.

Ehrlichman, R. S., M. J. Gandal, C. R. Maxwell, M. T. Lazarewicz, L. H. Finkel, D. Contreras, B. I. Turetsky and S. J. Siegel (2009). "N-methyl-d-aspartic acid receptor antagonist-induced frequency oscillations in mice recreate pattern of electrophysiological deficits in schizophrenia." Neuroscience 158(2): 705-712.

Elliot Hong, L., L. V. Moran, X. Du, P. O'Donnell and A. Summerfelt (2012). "Mismatch negativity and low frequency oscillations in schizophrenia families." Clin Neurophysiol 123(10): 1980-1988.

Ellison-Wright, I., D. C. Glahn, A. R. Laird, S. M. Thelen and E. Bullmore (2008). "The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis." Am J Psychiatry. 165(8): 1015-1023. doi: 1010.1176/appi.ajp.2008.07101562. Epub 07102008 Apr 07101561.

Emsley, R., B. Chiliza and L. Asmal (2013). "The evidence for illness progression after relapse in schizophrenia." Schizophr Res 148(1-3): 117-121.

Ethridge, L. E., J. P. Hamm, J. R. Shapiro, A. T. Summerfelt, S. K. Keedy, M. C. Stevens, G. Pearlson, C. A. Tamminga, N. N. Boutros, J. A. Sweeney, M. S. Keshavan, G. Thaker and B. A. Clementz (2012). "Neural activations during auditory oddball processing discriminating schizophrenia and psychotic bipolar disorder." Biol Psychiatry 72(9): 766-774.

Faget-Agius, C., L. Boyer, C. Lancon, R. Richieri, E. Fassio, E. Soulier, V. Chanoine, P. Auquier, J. P. Ranjeva and M. Guye (2013). "Structural and functional reorganization of working memory system during the first decade in schizophrenia. A cross-sectional study." Schizophr Res. 151(1-3): 48-60. doi: 10.1016/j.schres.2013.1010.1023. Epub 2013 Nov 1011.

Flint, J., N. Timpson and M. Munafo (2014). "Assessing the utility of intermediate phenotypes for genetic mapping of psychiatric disease." Trends Neurosci.

Ford, J. M., B. J. Roach, R. S. Hoffman and D. H. Mathalon (2008). "The dependence of P300 amplitude on gamma synchrony breaks down in schizophrenia." Brain Res 1235: 133-142.

Fountoulakis, K. N., S. Kasper, O. Andreassen, P. Blier, A. Okasha, E. Severus, M. Versiani, R. Tandon, H. J. Moller and E. Vieta (2012). "Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry." Eur Arch Psychiatry Clin Neurosci 262 Suppl 1: 1-48.

Frangou, S., T. Sharma, G. Alarcon, T. Sigmudsson, N. Takei, C. Binnie and R. M. Murray (1997). "The Maudsley Family Study, II: Endogenous event-related potentials in familial schizophrenia." Schizophr Res 23(1): 45-53.

Freedman, R., A. Olincy, R. G. Ross, M. C. Waldo, K. E. Stevens, L. E. Adler and S. Leonard (2003). "The genetics of sensory gating deficits in schizophrenia." Curr Psychiatry Rep 5(2): 155-161.

Freedman, R., M. Waldo, P. Bickford-Wimer and H. Nagamoto (1991). "Elementary neuronal dysfunctions in schizophrenia." Schizophr Res 4(2): 233-243.

Fritz, J. B., M. Elhilali, S. V. David and S. A. Shamma (2007). "Auditory attention--focusing the searchlight on sound." Curr Opin Neurobiol. 17(4): 437-455. Epub 2007 Aug 2021.

Fuentemilla, L., J. Marco-Pallares, T. F. Munte and C. Grau (2008). "Theta EEG oscillatory activity and auditory change detection." Brain Res 1220: 93-101.

Fujimoto, T., E. Okumura, K. Takeuchi, A. Kodabashi, H. Tanaka, T. Otsubo, K. Nakamura, M. Sekine, S. Kamiya, Y. Higashi, M. Tsuji, S. Shimooki and T. Tamura (2012). "Changes in Event-Related Desynchronization and Synchronization during the Auditory Oddball Task in Schizophrenia Patients." Open Neuroimag J 6: 26-36.

Furth, K. E., S. Mastwal, K. H. Wang, A. Buonanno and D. Vullhorst (2013). "Dopamine, cognitive function, and gamma oscillations: role of D4 receptors." Front Cell Neurosci 7: 102.

Fusar-Poli, P., S. Borgwardt, A. Bechdolf, J. Addington, A. Riecher-Rossler, F. Schultze-Lutter, M. Keshavan, S. Wood, S. Ruhrmann, L. J. Seidman, L. Valmaggia, T. Cannon, E. Velthorst, L. De Haan, B. Cornblatt, I. Bonoldi, M. Birchwood, T. McGlashan, W. Carpenter, P. McGorry, J. Klosterkotter, P. McGuire and A. Yung (2013). "The psychosis high-risk state: a comprehensive state-of-the-art review." JAMA Psychiatry 70(1): 107-120.

Fusar-Poli, P., G. Deste, R. Smieskova, S. Barlati, A. R. Yung, O. Howes, R. D. Stieglitz, A. Vita, P. McGuire and S. Borgwardt (2012). "Cognitive functioning in prodromal psychosis: a meta-analysis." Arch Gen Psychiatry 69(6): 562-571.

Fusar-Poli, P., R. Smieskova, M. J. Kempton, B. C. Ho, N. C. Andreasen and S. Borgwardt (2013). "Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies." Neurosci Biobehav Rev 37(8): 1680-1691.

Galderisi, S., A. Mucci, U. Volpe and N. Boutros (2009). "Evidence-based medicine and electrophysiology in schizophrenia." Clin EEG Neurosci 40(2): 62-77.

Gallinat, J., G. Winterer, C. S. Herrmann and D. Senkowski (2004). "Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing." Clin Neurophysiol 115(8): 1863-1874.

Gjini, K., C. Arfken and N. N. Boutros (2010). "Relationships between sensory "gating out" and sensory "gating in" of auditory evoked potentials in schizophrenia: a pilot study." Schizophr Res 121(1-3): 139-145.

Glahn, D. C., E. E. Knowles, D. R. McKay, E. Sprooten, H. Raventos, J. Blangero, Gottesman, II and L. Almasy (2014). "Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics." Am J Med Genet B Neuropsychiatr Genet 165B(2): 122-130.

Gonzalez-Burgos, G. and D. A. Lewis (2008). "GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia." Schizophr Bull 34(5): 944-961.

Gottesman, II and T. D. Gould (2003). "The endophenotype concept in psychiatry: etymology and strategic intentions." Am J Psychiatry 160(4): 636-645.

Gray, C. M., P. Konig, A. K. Engel and W. Singer (1989). "Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties." Nature 338(6213): 334-337.

Greenwood, T. A., N. R. Swerdlow, R. E. Gur, K. S. Cadenhead, M. E. Calkins, D. J. Dobie, R. Freedman, M. F. Green, R. C. Gur, L. C. Lazzeroni, K. H. Nuechterlein, A. Olincy, A. D. Radant, A. Ray,

N. J. Schork, L. J. Seidman, L. J. Siever, J. M. Silverman, W. S. Stone, C. A. Sugar, D. W. Tsuang, M. T. Tsuang, B. I. Turetsky, G. A. Light and D. L. Braff (2013). "Genome-wide linkage analyses of 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia." Am J Psychiatry 170(5): 521-532.

Groom, M. J., A. T. Bates, G. M. Jackson, T. G. Calton, P. F. Liddle and C. Hollis (2008). "Event-related potentials in adolescents with schizophrenia and their siblings: a comparison with attention-deficit/hyperactivity disorder." Biol Psychiatry 63(8): 784-792.

Gross, J. (2014). "Analytical methods and experimental approaches for electrophysiological studies of brain oscillations." J Neurosci Methods 228: 57-66.

Guntekin, B. and E. Basar (2015). "Review of evoked and event-related delta responses in the human brain." Int J Psychophysiol.

Haenschel, C., T. Baldeweg, R. J. Croft, M. Whittington and J. Gruzelier (2000). "Gamma and beta frequency oscillations in response to novel auditory stimuli: A comparison of human electroencephalogram (EEG) data with in vitro models." Proc Natl Acad Sci U S A 97(13): 7645-7650.

Haenschel, C., R. A. Bittner, J. Waltz, F. Haertling, M. Wibral, W. Singer, D. E. Linden and E. Rodriguez (2009). "Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia." J Neurosci 29(30): 9481-9489.

Haijma, S. V., N. Van Haren, W. Cahn, P. C. Koolschijn, H. E. Hulshoff Pol and R. S. Kahn (2013). "Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects." Schizophr Bull 39(5): 1129-1138.

Hall, M. H., F. Rijsdijk, M. Picchioni, K. Schulze, U. Ettinger, T. Toulopoulou, E. Bramon, R. M. Murray and P. Sham (2007). "Substantial shared genetic influences on schizophrenia and event-related potentials." Am J Psychiatry 164(5): 804-812.

Hall, M. H., K. Schulze, F. Rijsdijk, M. Picchioni, U. Ettinger, E. Bramon, R. Freedman, R. M. Murray and P. Sham (2006). "Heritability and reliability of P300, P50 and duration mismatch negativity." Behav Genet 36(6): 845-857.

Hall, M. H., K. Schulze, P. Sham, S. Kalidindi, C. McDonald, E. Bramon, D. L. Levy, R. M. Murray and F. Rijsdijk (2008). "Further evidence for shared genetic effects between psychotic bipolar disorder and P50 suppression: a combined twin and family study." Am J Med Genet B Neuropsychiatr Genet 147B(5): 619-627.

Hall, M. H., J. W. Smoller, N. R. Cook, K. Schulze, P. Hyoun Lee, G. Taylor, E. Bramon, M. J. Coleman, R. M. Murray, D. F. Salisbury and D. L. Levy (2012). "Patterns of deficits in brain function in bipolar disorder and schizophrenia: a cluster analytic study." Psychiatry Res 200(2-3): 272-280.

Hall, M. H., G. Taylor, D. F. Salisbury and D. L. Levy (2011). "Sensory gating event-related potentials and oscillations in schizophrenia patients and their unaffected relatives." Schizophr Bull 37(6): 1187-1199.

Hamilton, M. (1967). "Development of a rating scale for primary depressive illness." Br J Soc Clin Psychol 6(4): 278-296.

Hamm, J. P., L. E. Ethridge, J. R. Shapiro, M. C. Stevens, N. N. Boutros, A. T. Summerfelt, M. S. Keshavan, J. A. Sweeney, G. Pearlson, C. A. Tamminga, G. Thaker and B. A. Clementz (2012). "Spatiotemporal and frequency domain analysis of auditory paired stimuli processing in schizophrenia and bipolar disorder with psychosis." Psychophysiology 49(4): 522-530.

Hasan, A., T. Wobrock, C. Grefkes, M. Labusga, K. Levold, T. Schneider-Axmann, P. Falkai, H. Muller, J. Klosterkotter and A. Bechdolf (2012). "Deficient inhibitory cortical networks in antipsychotic-naive subjects at risk of developing first-episode psychosis and first-episode schizophrenia patients: a cross-sectional study." Biol Psychiatry. 72(9): 744-751. doi: 710.1016/j.biopsych.2012.1003.1005. Epub 2012 Apr 1012.

Herrmann, C. S., I. Frund and D. Lenz (2010). "Human gamma-band activity: a review on cognitive and behavioral correlates and network models." Neurosci Biobehav Rev 34(7): 981-992.

Higashima, M., T. Tsukada, T. Nagasawa, T. Oka, T. Okamoto, Y. Okamoto and Y. Koshino (2007). "Reduction in event-related alpha attenuation during performance of an auditory oddball task in schizophrenia." Int J Psychophysiol 65(2): 95-102.

Higuchi, Y., T. Sumiyoshi, T. Seo, T. Miyanishi, Y. Kawasaki and M. Suzuki (2013). "Mismatch negativity and cognitive performance for the prediction of psychosis in subjects with at-risk mental state." PLoS One 8(1): e54080.

Hong, L. E., A. Summerfelt, R. W. Buchanan, P. O'Donnell, G. K. Thaker, M. A. Weiler and A. C. Lahti (2010). "Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine." Neuropsychopharmacology 35(3): 632-640.

Hong, L. E., A. Summerfelt, R. P. McMahon, G. K. Thaker and R. W. Buchanan (2004). "Gamma/beta oscillation and sensory gating deficit in schizophrenia." Neuroreport 15(1): 155-159.

Hong, L. E., A. Summerfelt, B. D. Mitchell, R. P. McMahon, I. Wonodi, R. W. Buchanan and G. K. Thaker (2008). "Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate." Arch Gen Psychiatry 65(9): 1008-1016.

Hong, L. E., A. Summerfelt, B. D. Mitchell, P. O'Donnell and G. K. Thaker (2012). "A shared low-frequency oscillatory rhythm abnormality in resting and sensory gating in schizophrenia." Clin Neurophysiol 123(2): 285-292.

Howes, O. D. and S. Kapur (2009). "The dopamine hypothesis of schizophrenia: version III--the final common pathway." Schizophr Bull. 35(3): 549-562. doi: 510.1093/schbul/sbp1006. Epub 2009 Mar 1026.

Hsieh, M. H., J. C. Shan, W. L. Huang, W. C. Cheng, M. J. Chiu, F. S. Jaw, H. G. Hwu and C. C. Liu (2012). "Auditory event-related potential of subjects with suspected pre-psychotic state and first-episode psychosis." Schizophr Res 140(1-3): 243-249.

Hulshoff Pol, H. E. and R. S. Kahn (2008). "What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia." Schizophr Bull 34(2): 354-366.

Irani, F., S. Kalkstein, E. A. Moberg and P. J. Moberg (2011). "Neuropsychological performance in older patients with schizophrenia: a meta-analysis of cross-sectional and longitudinal studies." Schizophr Bull. 37(6): 1318-1326. doi: 1310.1093/schbul/sbq1057. Epub 2010 Jun 1314.

Jaaskelainen, I. P., J. Ahveninen, J. W. Belliveau, T. Raij and M. Sams (2007). "Short-term plasticity in auditory cognition." Trends Neurosci. 30(12): 653-661. Epub 2007 Nov 2005.

Jager, M., M. Riedel, T. Messer, G. Laux, H. Pfeiffer, D. Naber, L. G. Schmidt, W. Gaebel, W. Huff, I. Heuser, K. U. Kuhn, M. R. Lemke, E. Ruther, G. Buchkremer, M. Gastpar, R. Bottlender, A. Strauss and H. J. Moller (2007). "Psychopathological characteristics and treatment response of first episode compared with multiple episode schizophrenic disorders." Eur Arch Psychiatry Clin Neurosci 257(1): 47-53.

Jahshan, C., K. S. Cadenhead, A. J. Rissling, K. Kirihara, D. L. Braff and G. A. Light (2012). "Automatic sensory information processing abnormalities across the illness course of schizophrenia." Psychol Med 42(1): 85-97.

Jahshan, C., R. K. Heaton, S. Golshan and K. S. Cadenhead (2010). "Course of neurocognitive deficits in the prodrome and first episode of schizophrenia." Neuropsychology 24(1): 109-120.

Jansen, B. H., A. Hegde and N. N. Boutros (2004). "Contribution of different EEG frequencies to auditory evoked potential abnormalities in schizophrenia." Clin Neurophysiol 115(3): 523-533.

Javitt, D. C., K. M. Spencer, G. K. Thaker, G. Winterer and M. Hajos (2008). "Neurophysiological biomarkers for drug development in schizophrenia." Nat Rev Drug Discov 7(1): 68-83.

Jensen, O. and L. L. Colgin (2007). "Cross-frequency coupling between neuronal oscillations." Trends Cogn Sci 11(7): 267-269.

Johannesen, J. K., B. F. O'Donnell, A. Shekhar, J. H. McGrew and W. P. Hetrick (2013). "Diagnostic specificity of neurophysiological endophenotypes in schizophrenia and bipolar disorder." Schizophr Bull 39(6): 1219-1229.

Kahn, R. S., W. W. Fleischhacker, H. Boter, M. Davidson, Y. Vergouwe, I. P. Keet, M. D. Gheorghe, J. K. Rybakowski, S. Galderisi, J. Libiger, M. Hummer, S. Dollfus, J. J. Lopez-Ibor, L. G. Hranov, W.

Gaebel, J. Peuskens, N. Lindefors, A. Riecher-Rossler and D. E. Grobbee (2008). "Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial." Lancet 371(9618): 1085-1097.

Kapur, S. (2003). "Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia." Am J Psychiatry 160(1): 13-23.

Karakas, S. and E. Basar (1998). "Early gamma response is sensory in origin: a conclusion based on cross-comparison of results from multiple experimental paradigms." Int J Psychophysiol 31(1): 13-31.

Kay, S. R., A. Fiszbein and L. A. Opler (1987). "The positive and negative syndrome scale (PANSS) for schizophrenia." Schizophr Bull 13(2): 261-276.

Kayser, J., C. E. Tenke, C. J. Kroppmann, D. M. Alschuler, S. Fekri, S. Ben-David, C. M. Corcoran and G. E. Bruder (2014). "Auditory event-related potentials and alpha oscillations in the psychosis prodrome: neuronal generator patterns during a novelty oddball task." Int J Psychophysiol 91(2): 104-120.

Kegeles, L. S., A. Abi-Dargham, Y. Zea-Ponce, J. Rodenhiser-Hill, J. J. Mann, R. L. Van Heertum, T. B. Cooper, A. Carlsson and M. Laruelle (2000). "Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia." Biol Psychiatry 48(7): 627-640.

Kendler, K. S. and M. C. Neale (2010). "Endophenotype: a conceptual analysis." Mol Psychiatry 15(8): 789-797.

Keshavan, M. S. (1999). "Development, disease and degeneration in schizophrenia: a unitary pathophysiological model." J Psychiatr Res 33(6): 513-521.

Kim, M. A., E. Tura, S. G. Potkin, J. H. Fallon, D. S. Manoach, V. D. Calhoun and J. A. Turner (2010). "Working memory circuitry in schizophrenia shows widespread cortical inefficiency and compensation." Schizophr Res. 117(1): 42-51. doi: 10.1016/j.schres.2009.1012.1014. Epub 2010 Jan 1021.

Kindermann, S. S., G. G. Brown, L. E. Zorrilla, R. K. Olsen and D. V. Jeste (2004). "Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI." Schizophr Res. 68(2-3): 203-216.

Kirino, E. and R. Inoue (1999). "Relationship of mismatch negativity to background EEG and morphological findings in schizophrenia." Neuropsychobiology 40(1): 14-20.

Kirkpatrick, B., E. Messias, P. D. Harvey, E. Fernandez-Egea and C. R. Bowie (2008). "Is schizophrenia a syndrome of accelerated aging?" Schizophr Bull. 34(6): 1024-1032. Epub 2007 Dec 1021.

Kisley, M. A., T. L. Noecker and P. M. Guinther (2004). "Comparison of sensory gating to mismatch negativity and self-reported perceptual phenomena in healthy adults." Psychophysiology 41(4): 604-612.

Klimesch, W. (2012). "alpha-band oscillations, attention, and controlled access to stored information." Trends Cogn Sci 16(12): 606-617.

Knyazev, G. G. (2007). "Motivation, emotion, and their inhibitory control mirrored in brain oscillations." Neurosci Biobehav Rev 31(3): 377-395.

Koch, M., C. Schmiedt-Fehr and B. Mathes (2015). "Neuropharmacology of altered brain oscillations in schizophrenia." Int J Psychophysiol.

Koike, S., R. Takizawa, Y. Nishimura, M. Kinou, S. Kawasaki and K. Kasai (2013). "Reduced but broader prefrontal activity in patients with schizophrenia during n-back working memory tasks: a multi-channel near-infrared spectroscopy study." J Psychiatr Res. 47(9): 1240-1246. doi: 1210.1016/j.jpsychires.2013.1205.1009. Epub 2013 Jun 1243.

Lakatos, P., G. Karmos, A. D. Mehta, I. Ulbert and C. E. Schroeder (2008). "Entrainment of neuronal oscillations as a mechanism of attentional selection." Science 320(5872): 110-113.

Lawrie, S. M., H. C. Whalley, S. S. Abukmeil, J. N. Kestelman, L. Donnelly, P. Miller, J. J. Best, D. G. Owens and E. C. Johnstone (2001). "Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia." Biol Psychiatry. 49(10): 811-823.

Lee, K. H., L. M. Williams, A. Haig and E. Gordon (2003). ""Gamma (40 Hz) phase synchronicity" and symptom dimensions in schizophrenia." Cogn Neuropsychiatry 8(1): 57-71.

Leitman, D. I., P. Sehatpour, B. A. Higgins, J. J. Foxe, G. Silipo and D. C. Javitt (2010). "Sensory deficits and distributed hierarchical dysfunction in schizophrenia." Am J Psychiatry 167(7): 818-827.

Leonard, S., J. Gault, J. Hopkins, J. Logel, R. Vianzon, M. Short, C. Drebing, R. Berger, D. Venn, P. Sirota, G. Zerbe, A. Olincy, R. G. Ross, L. E. Adler and R. Freedman (2002). "Association of promoter variants in the alpha7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia." Arch Gen Psychiatry 59(12): 1085-1096.

Leon-Carrion, J., J. F. Martin-Rodriguez, J. Damas-Lopez, J. M. Barroso y Martin and M. R. Dominguez-Morales (2009). "Delta-alpha ratio correlates with level of recovery after neurorehabilitation in patients with acquired brain injury." Clin Neurophysiol 120(6): 1039-1045.

Leucht, S., J. M. Kane, W. Kissling, J. Hamann, E. Etschel and R. R. Engel (2005). "What does the PANSS mean?" Schizophr Res 79(2-3): 231-238.

Leung, M., C. Cheung, K. Yu, B. Yip, P. Sham, Q. Li, S. Chua and G. McAlonan (2011). "Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting." Schizophr Bull. 37(1): 199-211. doi: 110.1093/schbul/sbp1099. Epub 2009 Sep 1016.

Lewandowski, K. E., B. M. Cohen and D. Ongur (2011). "Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder." Psychol Med 41(2): 225-241.

Lewis, D. A., A. A. Curley, J. R. Glausier and D. W. Volk (2012). "Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia." Trends Neurosci 35(1): 57-67.

Lichtenstein, P., B. H. Yip, C. Bjork, Y. Pawitan, T. D. Cannon, P. F. Sullivan and C. M. Hultman (2009). "Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study." Lancet 373(9659): 234-239.

Lieberman, J., D. Jody, S. Geisler, J. Alvir, A. Loebel, S. Szymanski, M. Woerner and M. Borenstein (1993). "Time course and biologic correlates of treatment response in first-episode schizophrenia." Arch Gen Psychiatry 50(5): 369-376.

Lieberman, J. A. (1999). "Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective." Biol Psychiatry 46(6): 729-739.

Light, G. A., M. A. Geyer, B. A. Clementz, K. S. Cadenhead and D. L. Braff (2000). "Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications." Am J Psychiatry 157(5): 767-771.

Light, G. A., N. R. Swerdlow, A. J. Rissling, A. Radant, C. A. Sugar, J. Sprock, M. Pela, M. A. Geyer and D. L. Braff (2012). "Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia." PLoS One 7(7): e39434.

Light, G. A., N. R. Swerdlow, M. L. Thomas, M. E. Calkins, M. F. Green, T. A. Greenwood, R. E. Gur, R. C. Gur, L. C. Lazzeroni, K. H. Nuechterlein, M. Pela, A. D. Radant, L. J. Seidman, R. F. Sharp, L. J. Siever, J. M. Silverman, J. Sprock, W. S. Stone, C. A. Sugar, D. W. Tsuang, M. T. Tsuang, D. L. Braff and B. I. Turetsky (2015). "Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: Characterization of demographic, clinical, cognitive, and functional correlates in COGS-2." Schizophr Res 163(1-3): 63-72.

Lisman, J. E. and O. Jensen (2013). "The theta-gamma neural code." Neuron 77(6): 1002-1016.

Louchart-de la Chapelle, S., I. Nkam, E. Houy, A. Belmont, J. F. Menard, A. C. Roussignol, O. Siwek, M. Mezerai, M. Guillermou, G. Fouldrin, D. Levillain, S. Dollfus, D. Campion and F. Thibaut (2005). "A concordance study of three electrophysiological measures in schizophrenia." Am J Psychiatry 162(3): 466-474.

Luck, S. J., D. H. Mathalon, B. F. O'Donnell, M. S. Hamalainen, K. M. Spencer, D. C. Javitt and P. J. Uhlhaas (2011). "A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research." Biol Psychiatry 70(1): 28-34.

MacDonald, A. W., 3rd, H. W. Thermenos, D. M. Barch and L. J. Seidman (2009). "Imaging genetic liability to schizophrenia: systematic review of FMRI studies of patients' nonpsychotic relatives." Schizophr Bull. 35(6): 1142-1162. doi: 1110.1093/schbul/sbn1053. Epub 2008 Jun 1112.

Magno, E., S. Yeap, J. H. Thakore, H. Garavan, P. De Sanctis and J. J. Foxe (2008). "Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia." Biol Psychiatry 64(5): 385-391.

Makeig, S., S. Debener, J. Onton and A. Delorme (2004). "Mining event-related brain dynamics." Trends Cogn Sci 8(5): 204-210.

Malaspina, D. (2006). "Schizophrenia: a neurodevelopmental or a neurodegenerative disorder." J Clin Psychiatry 67(8): e07.

Maris, E. and R. Oostenveld (2007). "Nonparametric statistical testing of EEG- and MEG-data." J Neurosci Methods 164(1): 177-190.

Martin-Loeches, M., V. Molina, F. Munoz, J. A. Hinojosa, S. Reig, M. Desco, C. Benito, J. Sanz, A. Gabiri, F. Sarramea, A. Santos and T. Palomo (2001). "P300 amplitude as a possible correlate of frontal degeneration in schizophrenia." Schizophr Res 49(1-2): 121-128.

Mason, O., M. Startup, S. Halpin, U. Schall, A. Conrad and V. Carr (2004). "Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'." Schizophr Res 71(2-3): 227-237.

Mason, O. J. and F. Brady (2009). "The psychotomimetic effects of short-term sensory deprivation." J Nerv Ment Dis 197(10): 783-785.

Mathalon, D. H., J. M. Ford and A. Pfefferbaum (2000). "Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study." Biol Psychiatry 47(5): 434-449.

Mathalon, D. H., J. M. Ford, M. Rosenbloom and A. Pfefferbaum (2000). "P300 reduction and prolongation with illness duration in schizophrenia." Biol Psychiatry 47(5): 413-427.

Mazaheri, A. and T. W. Picton (2005). "EEG spectral dynamics during discrimination of auditory and visual targets." Brain Res Cogn Brain Res 24(1): 81-96.

McDonald, C., E. T. Bullmore, P. C. Sham, X. Chitnis, H. Wickham, E. Bramon and R. M. Murray (2004). "Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes." Arch Gen Psychiatry 61(10): 974-984.

McEvoy, J. P., G. E. Hogarty and S. Steingard (1991). "Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose." Arch Gen Psychiatry 48(8): 739-745.

McGorry, P. D., I. B. Hickie, A. R. Yung, C. Pantelis and H. J. Jackson (2006). "Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions." Aust N Z J Psychiatry 40(8): 616-622.

McGorry, P. D., E. Killackey and A. Yung (2008). "Early intervention in psychosis: concepts, evidence and future directions." World Psychiatry 7(3): 148-156.

Mechelli, A., A. Riecher-Rossler, E. M. Meisenzahl, S. Tognin, S. J. Wood, S. J. Borgwardt, N. Koutsouleris, A. R. Yung, J. M. Stone, L. J. Phillips, P. D. McGorry, I. Valli, D. Velakoulis, J. Woolley, C. Pantelis and P. McGuire (2011). "Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study." Arch Gen Psychiatry 68(5): 489-495.

Melara, R. D., A. Rao and Y. Tong (2002). "The duality of selection: excitatory and inhibitory processes in auditory selective attention." J Exp Psychol Hum Percept Perform. 28(2): 279-306.

Michie, P. T., H. Innes-Brown, J. Todd and A. V. Jablensky (2002). "Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders." Biol Psychiatry 52(7): 749-758.

Minzenberg, M. J., A. J. Firl, J. H. Yoon, G. C. Gomes, C. Reinking and C. S. Carter (2010). "Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia." Neuropsychopharmacology 35(13): 2590-2599.

Minzenberg, M. J., A. R. Laird, S. Thelen, C. S. Carter and D. C. Glahn (2009). "Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia." Arch Gen Psychiatry 66(8): 811-822.

Mirzakhanian, H., F. Singh, K. Seeber, K. M. Shafer and K. S. Cadenhead (2013). "A developmental look at the attentional system in the at risk and first episode of psychosis: age related changes in attention along the psychosis spectrum." Cogn Neuropsychiatry 18(1-2): 26-43.

Moran, L. V. and L. E. Hong (2011). "High vs low frequency neural oscillations in schizophrenia." Schizophr Bull 37(4): 659-663.

Moretti, D. V., D. Paternico, G. Binetti, O. Zanetti and G. B. Frisoni (2014). "EEG upper/low alpha frequency power ratio and the impulsive disorders network in subjects with mild cognitive impairment." Curr Alzheimer Res 11(2): 192-199.

Mueller, V., Y. Brehmer, T. von Oertzen, S. C. Li and U. Lindenberger (2008). "Electrophysiological correlates of selective attention: a lifespan comparison." BMC Neurosci 9: 18.

Murphy, J. R., C. Rawdon, I. Kelleher, D. Twomey, P. S. Markey, M. Cannon and R. A. Roche (2013). "Reduced duration mismatch negativity in adolescents with psychotic symptoms: further evidence for mismatch negativity as a possible biomarker for vulnerability to psychosis." BMC Psychiatry 13: 45.

Murray, R. M. and S. W. Lewis (1987). "Is schizophrenia a neurodevelopmental disorder?" Br Med J (Clin Res Ed). 295(6600): 681-682.

Murray, R. M., P. Sham, J. Van Os, J. Zanelli, M. Cannon and C. McDonald (2004). "A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder." Schizophr Res 71(2-3): 405-416.

Naatanen, R. and S. Kahkonen (2009). "Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review." Int J Neuropsychopharmacol 12(1): 125-135.

Naatanen, R., T. Kujala, C. Escera, T. Baldeweg, K. Kreegipuu, S. Carlson and C. Ponton (2012). "The mismatch negativity (MMN)--a unique window to disturbed central auditory processing in ageing and different clinical conditions." Clin Neurophysiol 123(3): 424-458.

Naatanen, R., T. Kujala and I. Winkler (2011). "Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses." Psychophysiology 48(1): 4-22.

Naatanen, R., P. Paavilainen, T. Rinne and K. Alho (2007). "The mismatch negativity (MMN) in basic research of central auditory processing: a review." Clin Neurophysiol 118(12): 2544-2590.

Nagamoto, H. T., L. E. Adler, M. C. Waldo and R. Freedman (1989). "Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval." Biol Psychiatry **25**(5): 549-561.

Narayan, S., B. Tang, S. R. Head, T. J. Gilmartin, J. G. Sutcliffe, B. Dean and E. A. Thomas (2008). "Molecular profiles of schizophrenia in the CNS at different stages of illness." Brain Res. 1239:235-48.(doi): 10.1016/j.brainres.2008.1008.1023. Epub 2008 Aug 1016.

Narayanan, B., K. O'Neil, C. Berwise, M. C. Stevens, V. D. Calhoun, B. A. Clementz, C. A. Tamminga, J. A. Sweeney, M. S. Keshavan and G. D. Pearlson (2014). "Resting state electroencephalogram oscillatory abnormalities in schizophrenia and psychotic bipolar patients and their relatives from the bipolar and schizophrenia network on intermediate phenotypes study." Biol Psychiatry 76(6): 456-465.

Nestor, P. G., M. Kubicki, K. M. Spencer, M. Niznikiewicz, R. W. McCarley and M. E. Shenton (2007). "Attentional networks and cingulum bundle in chronic schizophrenia." Schizophr Res 90(1-3): 308-315.

Neuper, C. and G. Pfurtscheller (2001). "Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates." Int J Psychophysiol 43(1): 41-58.

Nosarti, C., A. Reichenberg, R. M. Murray, S. Cnattingius, M. P. Lambe, L. Yin, J. MacCabe, L. Rifkin and C. M. Hultman (2012). "Preterm birth and psychiatric disorders in young adult life." Arch Gen Psychiatry 69(6): E1-8.

Nurnberger, J. I., Jr., M. C. Blehar, C. A. Kaufmann, C. York-Cooler, S. G. Simpson, J. Harkavy-Friedman, J. B. Severe, D. Malaspina and T. Reich (1994). "Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative." Arch Gen Psychiatry 51(11): 849-859; discussion 863-844.

Ogrim, G., J. Kropotov and K. Hestad (2012). "The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: sensitivity, specificity, and behavioral correlates." Psychiatry Res 198(3): 482-488.

Olabi, B., I. Ellison-Wright, A. M. McIntosh, S. J. Wood, E. Bullmore and S. M. Lawrie (2011). "Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies." Biol Psychiatry. 70(1): 88-96. doi: 10.1016/j.biopsych.2011.1001.1032. Epub 2011 Mar 1031.

Olincy, A., D. L. Braff, L. E. Adler, K. S. Cadenhead, M. E. Calkins, D. J. Dobie, M. F. Green, T. A. Greenwood, R. E. Gur, R. C. Gur, G. A. Light, J. Mintz, K. H. Nuechterlein, A. D. Radant, N. J. Schork, L. J. Seidman, L. J. Siever, J. M. Silverman, W. S. Stone, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang, B. I. Turetsky, B. D. Wagner and R. Freedman (2010). "Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the Consortium on Genetics of Schizophrenia." Schizophr Res 119(1-3): 175-182.

Ozgurdal, S., Y. Gudlowski, H. Witthaus, W. Kawohl, I. Uhl, M. Hauser, I. Gorynia, J. Gallinat, M. Heinze, A. Heinz and G. Juckel (2008). "Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia." Schizophr Res 105(1-3): 272-278.

Pantelis, C., M. Yucel, S. J. Wood, P. D. McGorry and D. Velakoulis (2003). "Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences." Aust N Z J Psychiatry 37(4): 399-406.

Park, D. C. and P. Reuter-Lorenz (2009). "The adaptive brain: aging and neurocognitive scaffolding." Annu Rev Psychol 60:173-96.(doi): 10.1146/annurev.psych.1159.103006.093656.

Patterson, J. V., W. P. Hetrick, N. N. Boutros, Y. Jin, C. Sandman, H. Stern, S. Potkin and W. E. Bunney, Jr. (2008). "P50 sensory gating ratios in schizophrenics and controls: a review and data analysis." Psychiatry Res 158(2): 226-247.

Penny, W. D., E. Duzel, K. J. Miller and J. G. Ojemann (2008). "Testing for nested oscillation." J Neurosci Methods 174(1): 50-61.

Pfurtscheller, G. and F. H. Lopes da Silva (1999). "Event-related EEG/MEG synchronization and desynchronization: basic principles." Clin Neurophysiol 110(11): 1842-1857.

Polich, J. (2007). "Updating P300: an integrative theory of P3a and P3b." Clin Neurophysiol 118(10): 2128-2148.

Potter, D., A. Summerfelt, J. Gold and R. W. Buchanan (2006). "Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia." Schizophr Bull 32(4): 692-700.

Price, G. W., P. T. Michie, J. Johnston, H. Innes-Brown, A. Kent, P. Clissa and A. V. Jablensky (2006). "A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia." Biol Psychiatry 60(1): 1-10.

Putman, P., B. Verkuil, E. Arias-Garcia, I. Pantazi and C. van Schie (2014). "EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention." Cogn Affect Behav Neurosci 14(2): 782-791.

Rabinowitz, N. C., B. D. Willmore, J. W. Schnupp and A. J. King (2011). "Contrast gain control in auditory cortex." Neuron. 70(6): 1178-1191. doi: 1110.1016/j.neuron.2011.1104.1030.

Ranlund, S., J. Nottage, M. Shaikh, A. Dutt, M. Constante, M. Walshe, M. H. Hall, K. Friston, R. Murray and E. Bramon (2014). "Resting EEG in psychosis and at-risk populations--a possible endophenotype?" Schizophr Res 153(1-3): 96-102.

Rapoport, J. L., J. N. Giedd and N. Gogtay (2012). "Neurodevelopmental model of schizophrenia: update 2012." Mol Psychiatry 17(12): 1228-1238.

Reichenberg, A., A. Caspi, H. Harrington, R. Houts, R. S. Keefe, R. M. Murray, R. Poulton and T. E. Moffitt (2010). "Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study." Am J Psychiatry 167(2): 160-169.

Roach, B. J. and D. H. Mathalon (2008). "Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia." Schizophr Bull 34(5): 907-926.

Rosburg, T., P. Trautner, C. E. Elger and M. Kurthen (2009). "Attention effects on sensory gating--intracranial and scalp recordings." Neuroimage 48(3): 554-563.

Roschke, J. and J. Fell (1997). "Spectral analysis of P300 generation in depression and schizophrenia." Neuropsychobiology 35(2): 108-114.

Roth, W. T. and E. H. Cannon (1972). "Some features of the auditory evoked response in schizophrenics." Arch Gen Psychiatry 27(4): 466-471.

Salisbury, D. F., N. Kuroki, K. Kasai, M. E. Shenton and R. W. McCarley (2007). "Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia." Arch Gen Psychiatry 64(5): 521-529.

Salisbury, D. F., M. E. Shenton, A. R. Sherwood, I. A. Fischer, D. A. Yurgelun-Todd, M. Tohen and R. W. McCarley (1998). "First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe." Arch Gen Psychiatry 55(2): 173-180.

Sangal, R. B. and J. M. Sangal (2014). "Use of EEG Beta-1 Power and Theta/Beta Ratio Over Broca's Area to confirm Diagnosis of Attention Deficit/Hyperactivity Disorder in Children." Clin EEG Neurosci.

Sauseng, P., W. Klimesch, W. R. Gruber, S. Hanslmayr, R. Freunberger and M. Doppelmayr (2007). "Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion." Neuroscience 146(4): 1435-1444.

Schleiger, E., N. Sheikh, T. Rowland, A. Wong, S. Read and S. Finnigan (2014). "Frontal EEG delta/alpha ratio and screening for post-stroke cognitive deficits: the power of four electrodes." Int J Psychophysiol 94(1): 19-24.

Schmiedt, C., A. Brand, H. Hildebrandt and C. Basar-Eroglu (2005). "Event-related theta oscillations during working memory tasks in patients with schizophrenia and healthy controls." Brain Res Cogn Brain Res 25(3): 936-947.

Schulze, K. K., M. H. Hall, C. McDonald, N. Marshall, M. Walshe, R. M. Murray and E. Bramon (2007). "P50 auditory evoked potential suppression in bipolar disorder patients with psychotic features and their unaffected relatives." Biol Psychiatry 62(2): 121-128.

Schulze, K. K., M. H. Hall, C. McDonald, N. Marshall, M. Walshe, R. M. Murray and E. Bramon (2008). "Auditory P300 in patients with bipolar disorder and their unaffected relatives." Bipolar Disord 10(3): 377-386.

Schwartz, T. L., S. Sachdeva and S. M. Stahl (2012). "Glutamate neurocircuitry: theoretical underpinnings in schizophrenia." Front Pharmacol 3: 195.

Seidman, L. J., A. J. Giuliano, E. C. Meyer, J. Addington, K. S. Cadenhead, T. D. Cannon, T. H. McGlashan, D. O. Perkins, M. T. Tsuang, E. F. Walker, S. W. Woods, C. E. Bearden, B. K. Christensen, K. Hawkins, R. Heaton, R. S. Keefe, R. Heinssen and B. A. Cornblatt (2010). "Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis." Arch Gen Psychiatry 67(6): 578-588.

Shaikh, M., M. H. Hall, K. Schulze, A. Dutt, K. Li, I. Williams, M. Walshe, M. Constante, M. Broome, M. Picchioni, T. Toulopoulou, D. Collier, D. Stahl, F. Rijsdijk, J. Powell, R. M. Murray, M. Arranz and

E. Bramon (2013). "Effect of DISC1 on the P300 waveform in psychosis." Schizophr Bull 39(1): 161-167.

Shelley, A. M., P. B. Ward, S. V. Catts, P. T. Michie, S. Andrews and N. McConaghy (1991). "Mismatch negativity: an index of a preattentive processing deficit in schizophrenia." Biol Psychiatry 30(10): 1059-1062.

Shinn-Cunningham, B. G. (2008). "Object-based auditory and visual attention." Trends Cogn Sci. 12(5): 182-186. doi: 110.1016/j.tics.2008.1002.1003. Epub 2008 Apr 1017.

Siegel, C., M. Waldo, G. Mizner, L. E. Adler and R. Freedman (1984). "Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses." Arch Gen Psychiatry 41(6): 607-612.

Siekmeier, P. J. and S. M. Stufflebeam (2010). "Patterns of spontaneous magnetoencephalographic activity in patients with schizophrenia." J Clin Neurophysiol 27(3): 179-190.

Smith, A. K., J. C. Edgar, M. Huang, B. Y. Lu, R. J. Thoma, F. M. Hanlon, G. McHaffie, A. P. Jones, R. D. Paz, G. A. Miller and J. M. Canive (2010). "Cognitive abilities and 50- and 100-msec paired-click processes in schizophrenia." Am J Psychiatry 167(10): 1264-1275.

Spencer, K. M., P. G. Nestor, R. Perlmutter, M. A. Niznikiewicz, M. C. Klump, M. Frumin, M. E. Shenton and R. W. McCarley (2004). "Neural synchrony indexes disordered perception and cognition in schizophrenia." Proc Natl Acad Sci U S A 101(49): 17288-17293.

Spencer, K. M., D. F. Salisbury, M. E. Shenton and R. W. McCarley (2008). "Gamma-band auditory steady-state responses are impaired in first episode psychosis." Biol Psychiatry 64(5): 369-375.

Stafford, M. R., H. Jackson, E. Mayo-Wilson, A. P. Morrison and T. Kendall (2013). "Early interventions to prevent psychosis: systematic review and meta-analysis." BMJ 346: f185.

Staikou, C., A. Kyrozis, C. Moschovos and A. Fassoulaki (2012). "Effects of morning melatonin administration on electroencephalographic theta to alpha power ratio in reproductive versus postmenopausal healthy female volunteers." Neurosci Lett 507(1): 90-93.

Stone, J. M., P. D. Morrison and L. S. Pilowsky (2007). "Glutamate and dopamine dysregulation in schizophrenia--a synthesis and selective review." J Psychopharmacol 21(4): 440-452.

Sun, L., N. Castellanos, C. Grutzner, D. Koethe, D. Rivolta, M. Wibral, L. Kranaster, W. Singer, M. F. Leweke and P. J. Uhlhaas (2013). "Evidence for dysregulated high-frequency oscillations during sensory processing in medication-naive, first episode schizophrenia." Schizophr Res 150(2-3): 519-525.

Sutton, S., M. Braren, J. Zubin and E. R. John (1965). "Evoked-potential correlates of stimulus uncertainty." Science 150(3700): 1187-1188.

Szoke, A., A. Trandafir, M. E. Dupont, A. Meary, F. Schurhoff and M. Leboyer (2008). "Longitudinal studies of cognition in schizophrenia: meta-analysis." Br J Psychiatry 192(4): 248-257.

Tallon-Baudry, C. (2009). "The roles of gamma-band oscillatory synchrony in human visual cognition." Front Biosci (Landmark Ed) 14: 321-332.

Tallon-Baudry, C., O. Bertrand, C. Delpuech and J. Pernier (1996). "Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human." J Neurosci 16(13): 4240-4249.

Tamminga, C. A., E. I. Ivleva, M. S. Keshavan, G. D. Pearlson, B. A. Clementz, B. Witte, D. W. Morris, J. Bishop, G. K. Thaker and J. A. Sweeney (2013). "Clinical Phenotypes of Psychosis in the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP)." Am J Psychiatry.

Tan, H. Y., J. H. Callicott and D. R. Weinberger (2007). "Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia." Cereb Cortex. 17(Suppl 1): i171-181.

Tandon, R., W. Gaebel, D. M. Barch, J. Bustillo, R. E. Gur, S. Heckers, D. Malaspina, M. J. Owen, S. Schultz, M. Tsuang, J. Van Os and W. Carpenter (2013). "Definition and description of schizophrenia in the DSM-5." Schizophr Res 150(1): 3-10.

Tandon, R., H. A. Nasrallah and M. S. Keshavan (2009). "Schizophrenia, “just the facts” 4. Clinical features and conceptualization." Schizophrenia Research 110(1–3): 1-23.

Thaker, G. K. (2008). "Neurophysiological endophenotypes across bipolar and schizophrenia psychosis." Schizophr Bull 34(4): 760-773.

Thompson, W. K., G. N. Savla, I. V. Vahia, C. A. Depp, R. O'Hara, D. V. Jeste and B. W. Palmer (2013). "Characterizing trajectories of cognitive functioning in older adults with schizophrenia: does method matter?" Schizophr Res 143(1): 90-96.

Todd, J., P. T. Michie, U. Schall, P. B. Ward and S. V. Catts (2012). "Mismatch negativity (MMN) reduction in schizophrenia-impaired prediction--error generation, estimation or salience?" Int J Psychophysiol 83(2): 222-231.

Traub, R. D., M. A. Whittington, E. H. Buhl, J. G. Jefferys and H. J. Faulkner (1999). "On the mechanism of the gamma --> beta frequency shift in neuronal oscillations induced in rat hippocampal slices by tetanic stimulation." J Neurosci 19(3): 1088-1105.

Tsuang, M. T., J. Van Os, R. Tandon, D. M. Barch, J. Bustillo, W. Gaebel, R. E. Gur, S. Heckers, D. Malaspina, M. J. Owen, S. Schultz and W. Carpenter (2013). "Attenuated psychosis syndrome in DSM-5." Schizophr Res 150(1): 31-35.

Turetsky, B. I., W. B. Bilker, S. J. Siegel, C. G. Kohler and R. E. Gur (2009). "Profile of auditory information-processing deficits in schizophrenia." Psychiatry Res 165(1-2): 27-37.

Turetsky, B. I., M. E. Calkins, G. A. Light, A. Olincy, A. D. Radant and N. R. Swerdlow (2007). "Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures." Schizophr Bull 33(1): 69-94.

Turetsky, B. I., T. D. Cannon and R. E. Gur (2000). "P300 subcomponent abnormalities in schizophrenia: III. Deficits In unaffected siblings of schizophrenic probands." Biol Psychiatry 47(5): 380-390.

Turetsky, B. I., E. M. Dress, D. L. Braff, M. E. Calkins, M. F. Green, T. A. Greenwood, R. E. Gur, R. C. Gur, L. C. Lazzeroni, K. H. Nuechterlein, A. D. Radant, L. J. Seidman, L. J. Siever, J. M. Silverman, J. Sprock, W. S. Stone, C. A. Sugar, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang and G. Light (2015). "The utility of P300 as a schizophrenia endophenotype and predictive biomarker: Clinical and socio-demographic modulators in COGS-2." Schizophr Res 163(1-3): 53-62.

Turrigiano, G. G. and S. B. Nelson (2004). "Homeostatic plasticity in the developing nervous system." Nat Rev Neurosci 5(2): 97-107.

Uhlhaas, P. J., C. Haenschel, D. Nikolic and W. Singer (2008). "The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia." Schizophr Bull 34(5): 927-943.

Uhlhaas, P. J. and W. Singer (2010). "Abnormal neural oscillations and synchrony in schizophrenia." Nat Rev Neurosci 11(2): 100-113.

Uhlhaas, P. J. and W. Singer (2012). "Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks." Neuron 75(6): 963-980.

Ulanovsky, N., L. Las and I. Nelken (2003). "Processing of low-probability sounds by cortical neurons." Nat Neurosci. 6(4): 391-398.

Umbricht, D. and S. Krljes (2005). "Mismatch negativity in schizophrenia: a meta-analysis." Schizophr Res 76(1): 1-23.

Umbricht, D. S., J. A. Bates, J. A. Lieberman, J. M. Kane and D. C. Javitt (2006). "Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia." Biol Psychiatry 59(8): 762-772.

van den Heuvel, M. P., O. Sporns, G. Collin, T. Scheewe, R. C. Mandl, W. Cahn, J. Goni, H. E. Hulshoff Pol and R. S. Kahn (2013). "Abnormal rich club organization and functional brain dynamics in schizophrenia." JAMA Psychiatry 70(8): 783-792.

van der Stelt, O. and A. Belger (2007). "Application of electroencephalography to the study of cognitive and brain functions in schizophrenia." Schizophr Bull 33(4): 955-970.

van der Stelt, O., J. A. Lieberman and A. Belger (2005). "Auditory P300 in high-risk, recent-onset and chronic schizophrenia." Schizophr Res 77(2-3): 309-320.

van Dinteren, R., M. Arns, M. L. Jongsma and R. P. Kessels (2014). "P300 development across the lifespan: a systematic review and meta-analysis." PLoS One 9(2): e87347.

van Tricht, M. J., D. H. Nieman, J. H. Koelman, L. J. Bour, J. N. van der Meer, T. A. van Amelsvoort, D. H. Linszen and L. de Haan (2011). "Auditory ERP components before and after transition to a first psychotic episode." Biol Psychol 87(3): 350-357.

van Tricht, M. J., D. H. Nieman, J. T. Koelman, A. J. Mensink, L. J. Bour, J. N. van der Meer, T. A. van Amelsvoort, D. H. Linszen and L. de Haan (2012). "Sensory gating in subjects at ultra high risk for developing a psychosis before and after a first psychotic episode." World J Biol Psychiatry.

Venables, N. C., E. M. Bernat and S. R. Sponheim (2009). "Genetic and disorder-specific aspects of resting state EEG abnormalities in schizophrenia." Schizophr Bull 35(4): 826-839.

Vohringer, P. A., S. A. Barroilhet, A. Amerio, M. L. Reale, K. Alvear, D. Vergne and S. N. Ghaemi (2013). "Cognitive impairment in bipolar disorder and schizophrenia: a systematic review." Front Psychiatry 4: 87.

von Stein, A., C. Chiang and P. Konig (2000). "Top-down processing mediated by interareal synchronization." Proc Natl Acad Sci U S A 97(26): 14748-14753.

von Stein, A. and J. Sarnthein (2000). "Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization." Int J Psychophysiol 38(3): 301-313.

Weinberger, D. R. (1987). "Implications of normal brain development for the pathogenesis of schizophrenia." Arch Gen Psychiatry. 44(7): 660-669.

Weiser, M. (2011). "Early intervention for schizophrenia: the risk-benefit ratio of antipsychotic treatment in the prodromal phase." Am J Psychiatry 168(8): 761-763.

Winterer, G., M. F. Egan, T. Raedler, C. Sanchez, D. W. Jones, R. Coppola and D. R. Weinberger (2003). "P300 and genetic risk for schizophrenia." Arch Gen Psychiatry 60(11): 1158-1167.

Wood, S. J., C. Pantelis, D. Velakoulis, M. Yucel, A. Fornito and P. D. McGorry (2008). "Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk." Schizophr Bull. 34(2): 322-329. doi: 310.1093/schbul/sbm1149. Epub 2008 Jan 1016.

Woodberry, K. A., W. R. McFarlane, A. J. Giuliano, M. B. Verdi, W. L. Cook, S. V. Faraone and L. J. Seidman (2013). "Change in neuropsychological functioning over one year in youth at clinical high risk for psychosis." Schizophr Res 146(1-3): 87-94.

Woods, B. T. (1998). "Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism." Am J Psychiatry 155(12): 1661-1670.

Wyatt, N. and L. Machado (2013). "Evidence inhibition responds reactively to the salience of distracting information during focused attention." PLoS One. 8(4): e62809. doi: 62810.61371/journal.pone.0062809. Print 0062013.

Yordanova, J., M. Devrim, V. Kolev, A. Ademoglu and T. Demiralp (2000). "Multiple time-frequency components account for the complex functional reactivity of P300." Neuroreport 11(5): 1097-1103.

Yordanova, J., V. Kolev and J. Polich (2001). "P300 and alpha event-related desynchronization (ERD)." Psychophysiology 38(1): 143-152.

Yung, A. R., L. J. Phillips, H. P. Yuen, S. M. Francey, C. A. McFarlane, M. Hallgren and P. D. McGorry (2003). "Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group." Schizophr Res 60(1): 21-32.

Yung, A. R., H. P. Yuen, G. Berger, S. Francey, T. C. Hung, B. Nelson, L. Phillips and P. McGorry (2007). "Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk?" Schizophr Bull 33(3): 673-681.

Yuval-Greenberg, S., O. Tomer, A. S. Keren, I. Nelken and L. Y. Deouell (2008). "Transient induced gamma-band response in EEG as a manifestation of miniature saccades." Neuron 58(3): 429-441.

Zipursky, R. B., T. J. Reilly and R. M. Murray (2013). "The myth of schizophrenia as a progressive brain disease." Schizophr Bull 39(6): 1363-1372.